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THE NEW YORK ACADEMY
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JULY 1939

THE SIGNIFICANCE TO MEDICINE OF PRESENT POPULATION TRENDS*

The Hermann Michael Biggs Memorial Lecture

FREDERICK OSBORN

WE ARE met to honor the name of one who left his distinguished mark on medical practice in this country. The forward-looking quality of his work is evidence that he would have desired that these lectures should provide from time to time an occasion for the members of his profession to consider the problems created by a changing world. It must have been in the minds of those who proposed the subject of this evening's discussion that Dr. Hermann Biggs would have been one of the first to recognize that the cumulative decline in births in recent years presents new problems and suggests added functions for those engaged in the practice of medicine.

We are at a major turning point in human biology. Following on a period of unprecedented numerical increase, European peoples appear headed for a serious decline. During a million or more years of existence, mankind slowly and with innumerable setbacks increased his numbers until by 1650 he attained the respectable figure of over 500 million persons, of whom 100 million were Europeans. Then, at an accelerating

* Read April 6, 1939 at The New York Academy of Medicine.

rate, births exceeded deaths, until in the early nineteen hundreds the increase of the white race reached its peak, a rate of increase of 40 per cent per generation (about 12.8 per 1000 per year). By 1933, Europeans and their descendants numbered 700 million,* a sevenfold increase in ten generations, while the human race as a whole had increased almost four times to something over 2 billion.

In the United States, the ten years, 1920-1930, marked the greatest addition to our numbers of any decade in American history, over 17 million people. Yet, coincident with this unexampled proliferation of the human species, there were unnoticed forces working towards a reversal of these trends. For a hundred years births per married women had been on the decline. After 1900, this decline became more rapid, but was hidden for a time by a remarkable decline in deaths, the excess of births above deaths remaining high. Thus, by 1932, while the crude birth rate had dropped to 17.4 per thousand, the crude death rate was only 10.9 per thousand, leaving a crude rate of natural increase of 6.5 per thousand per year. But in the same year, 1932, for the first time in our history, the women of childbearing age in the United States were failing to have enough children to replace their own number in the next generation.

Crude Versus Intrinsic Rates of Increase

In order to understand this paradox, it is necessary to have a clear picture of the difference between "crude" rates, as ordinarily reported, and "true" or "intrinsic" rates as used by students of population. Crude rates are rates of births or deaths per thousand of the population. The difference between these births and deaths is the crude rate of natural increase. Thus, if the crude birth rate is 17 per thousand of population per year, and the crude death rate is 11 per thousand of population per year, the crude rate of increase is the difference between the two, or 6 per thousand of population per year. These were approximately the rates for the United States in 1935. From these rates it would appear that the population is increasing rapidly. But if only 11 people out of every thousand died each year in a population with stabilized age distribution, the average length of life would be about 90 years, which is quite contrary to the known facts, the average span of life for our total population (White and Negro) being about 61 years. The crude death rate of 11 per thousand is so low because the present population of the United States,

* Estimate by Beloch as revised by Caviagnac.[1]

as a result of changing rates of fertility and mortality and immigration, contains an unusually high proportion of people in the middle age groups where death is least frequent. When the passage of time has corrected this proportion we can hardly expect a crude death rate of less than 15 per thousand, which would be appropriate to an expectation of life of sixty-six years, five years more than our present average.

Birth rates also are affected by the present high proportion of young adults in the childbearing ages; there are naturally more children born each year per thousand of population when the proportion of young adults is high, than would be the case if the proportion of non-childbearing old people were larger. Crude rates of reproduction are, therefore, a poor index of future trends.

Evidently we want to know whether the women of childbearing age are at any given time having enough children to replace their own number in the next generation. Statisticians can figure out the answer provided they have available vital statistics which show for any given year the number of children born to women in each age group during the childbearing period, and the death rates for each age, from birth to death.

From these specific rates are obtained gross and net reproduction ratios and, after taking into account the average interval between births in two successive generations, intrinsic rates of natural increase.

These new methods of ascertaining intrinsic rates of reproduction make it possible to forecast quite accurately the changes which will take place in a population for a generation ahead, if we omit consideration of immigration. The children born today will, subject to prevailing mortality rates, be the parents of the children born 30 years hence, just as they will also be the candidates for Townsend benefits about the year 2005. Thus, short-term forecasts covering not more than a generation can be made with considerable accuracy. Estimates over a longer term depend chiefly on the assumptions made about future birth rates. Death rates are less important to such estimates. At the time of the last census, 89 per cent of the white females born alive lived to the center of the reproductive period,[2] a loss of only 11 per cent due to mortality. Thus, today births and not deaths are the primary factor in selection for survival.

The Decline in Births

The population study of the National Resources Committee in 1938 presents estimates by Thompson and Whelpton of the future growth

of this country on three different assumptions of low, medium, and high fertility. On the assumption of low fertility, with no immigration, the maximum population would be 140 million, reached in 1960. On the assumption of medium fertility, the maximum would be 153 million reached in 1980.

For the past several years every new estimate has shortened the time remaining before the peak of population will have been reached and the decline in gross numbers will commence to set in. At present the intrinsic rate of reproduction is about .95; five per cent short of the rate required for replacement. This rate would be even lower if it were not for the high birth rate in the rural sections of the country. But the high rate in rural states is falling, and there is no sign of an increase in the urban states which are already far below the replacement level.

In much of Europe the decline in births began earlier and has gone farther. England had a net rate of reproduction of .76 in 1936, 24 per cent short of replacement; France, a net rate of .87 in 1935; Germany a net rate of .88 in 1935, after having been as low as .70 in 1933; Sweden a net rate of .70 in 1934.[3]

In the United States the decline in births is closely related to a growing urbanization. Cities of over 100,000 have a net rate of .75, twenty-five per cent short of the rate required for replacement. Cities down to 25,000 of population, and towns of 25,000 to 10,000 people, show rates of .88 and .97 respectively, just short of replacement. The small town breaks even with a rate of 1.04. Only the rural village, with a rate of 1.37, and the rural farm, with a rate of 1.69, are making substantial contributions to an increase of population. Because farmers in the South are so numerous and so prolific, their children will largely inherit what remains of the urban civilization we are trying to build.

Variations in birth rates with size of community result in interesting racial variations in reproduction. The Jews, who are concentrated in metropolitan centers, with high educational standards, are probably fifty per cent short of having enough children to replace their number in the next generation. Anglo-Saxons, because they are so numerous in the isolated, rural sections of the South, are more than holding their own. Negroes, about equally balanced between city and country, show the same rate of reproduction as does the country as a whole. Mexicans and Indians, the most isolated of all our peoples, are almost doubling their number in each generation.

Decline in the Proportion of Large Families

Wide differences in net rates of reproduction are very largely due to differences in the proportion of large families. In California, with the lowest rate of reproduction of any State in the Union, only 10.1 per cent of the families of fertile married women consisted of five or more children even prior to 1928.[4] In North Carolina, a State near the top of the reproductive list, 32.4 per cent of the fertile married women had five children or more, three times the proportion prevailing in California. And in English marriages of 1860 and 1870, one-half of the women had five children or more, with an average of eight children.

To maintain our present population would require something over 2.6 children per married woman. Taking into consideration the number of sterile marriages, we find that fertile couples must have on an average over three children to provide population replacement. But since not all fertile couples will have three children, some must have four and some five children to bring the average up to three. Almost any way we figure, we find that approximately 20 per cent of married women must have five or more children if the reproduction of the population is to be at a rate sufficient for replacement. And under the conditions of life in our cities and towns, nothing like 20 per cent of married women actually have families of five or more children. Among most professional groups, such large families are looked on askance.

In seventy years the proportion of these large families in our cities has fallen from 50 per cent to about 10 per cent. Is this due to a physiological inability to bear many children, brought about by the strain of modern life, or is it the result of a deliberate restriction of size of family? All available evidence points to the conclusion that voluntary control of family size has been the principal factor in the decline in births. Recent studies by Pearl[5] offer almost overwhelming proof to this effect. Among 30,000 women studied in hospitals in the eastern part of the United States, women practicing family limitation most intelligently and consistently had pregnancy rates from 50 to 75 per cent below those who reported no such efforts whatever. Among the women who reported no attempts to limit their families since marriage there appeared to be no significant difference in pregnancy rates, whatever their economic status or the size of community in which they lived. To quote Pearl's conclusions:

"In the population of the United States, at least, the fertility

differentials relative to race (Negro versus White) and to the three most important social class differentiations (economic, educational, and religious) are due primarily to differences in the relative prevalence and effectiveness of the efforts made to prevent conception, correlatively aided by relative frequency and postponement of marriage and the practice of criminal abortion, and to practically nothing else."

The use of birth control and the deliberate effort to restrict size of family is only a manifestation of underlying attitudes and customs. The decline in births is the result of numerous and complex causes. Any considerable increase in reproduction will probably depend on quite profound changes in economic and social relationships and on changes in personal values and attitudes toward family life.

This brief analysis has interesting implications for the medical profession. At present this country is well populated and thoughtful people would look on a reasonable decline in numbers with equanimity. But it is almost certain that with the extension of birth control services, an extension which seems inevitable and is almost certainly desirable, our net rate of reproduction will fall to .70 or less. At a level 30 per cent or more below the rate needed for replacement—and that is the direction we are headed for in the country as a whole—and a much lower rate for people at the high school level, there will be strong social reasons for bringing up the rate of reproduction at least to the replacement level among the more competent people who make use of the doctor's services. Doctors will feel the pressure of the demand for an increase in births and they will find that such an increase will depend very little on the science of medicine as it may effect a decrease in sterility, but very largely on the personal relations of the physician with each individual family through which he may influence their attitudes and their desire for children. And among a substantial proportion of couples the desire for children must extend beyond the one or two children who are supposed to satisfy the maternal instinct of modern women. Without numerous families of four or more children, reproduction will never approach the replacement rate.

Natural Selection is Still Effective

If the decline in births is the result of cultural factors under man's control, it is equally true that the accompanying decline in deaths is the

result of consciously directed efforts, particularly those of the medical profession. Some biologists have claimed that these artificial and man-made conditions have limited the force of natural selection and increased the reproduction of the weak and unfit. The evidence on this point is far from conclusive. Expectation of life at birth has increased from 49.2 years in 1900-1902 to 60.3 in 1929-1931. About four-fifths of this saving is due to the decrease of deaths between birth and the center of the reproductive period. The proportion of infants who live to reproduce is therefore much greater today than it was even a few decades ago. The predominant factor in this change has of course been the control of infectious diseases. In 1901, 12.4 per cent of all infants died in the first year of life, as compared to 5.8 per cent by 1930, a reduction of one-half in the death rate in thirty years. But during this period, deaths in the first month were reduced by only a fraction, from 4.1 per cent in 1901 to 3.1 per cent in 1930, while deaths in the next eleven months declined from 8.3 per cent in 1901 to 2.7 per cent in 1930.

The reduction in deaths after the first months certainly appears to be due chiefly to improvements in feeding and medical care, with relatively small relation to variations in known hereditary qualities. But deaths in the first month would appear more largely due to either parental or hereditary causes. The fact that births in the first month show a relatively small decline, seems to indicate that natural selection is still operating. In view of the recent extension of medical and public health measures, it is probable that improper care of expectant mothers and accidents of birth will play a still smaller part than in the past in causing the death of newborn infants, and that hereditary conditions will be even more important than previously.

Not only has there been little progress in reducing deaths among newborn infants, but equal difficulties have been found in combating the diseases of old age. In the organic and degenerative diseases of old age hereditary factors are also known to play a large role. We would expect this to be the case. These diseases rarely affect people until they have completed their reproductive period, so that the force of natural selection has not had a chance to eliminate such strains. But here, too, previous infections and improper conditions of life are responsible for a vast amount of preventable suffering and untimely death.

Medical science does undoubtedly in some cases save the lives of individuals with serious hereditary handicaps. In so far as the persons

saved may later have children themselves, there may result an accumulation of genetic factors that will cause greater hazards, costs and suffering for future generations. It is desirable therefore that progress in medicine be accompanied by progress in human genetics and social science, making possible the isolation of specific pathological factors, an understanding of hereditary mechanisms, and a humane program designed with reference both to the immediate physical and psychological needs of affected individuals and the more ultimate objectives of public health. Natural selection is still the major force for eliminating extreme deviations. But in proportion as it is the proper business of physicians to oppose untimely deaths as a factor in natural selection, so it is the physician's responsibility to use all his influence to limit conception among those who may be properly suspected as being carriers of serious hereditary defect. This is a new function for the doctor and one he is reluctant to assume. But it flows inevitably from the doctor's new control over death, and from man's increasing power to regulate births, and there is no one but the physician whom the public will or should trust for advice on so vital and personal a matter. If this new function is to be properly discharged, there must be a great increase in research in human genetics, and the results of such research must be rapidly assimilated by the medical profession.

Mental Diseases

Fortunately, the death rates of persons suffering from mental disease are far higher than those for persons of similar age in the general population. Even with modern institutional care and in the case of mental diseases that do not involve any known physical disorders, the death rates of the insane are extremely high. This is shown by a comparison of standardized death rates for mental patients and total population in New York State.

A comprehensive investigation of factors affecting the net reproduction of the mentally diseased has recently been published by a Swedish scholar, using data on schizophrenia (dementia praecox), manic-depressive psychosis, and epilepsy, drawn from the archives of the Kaiser-Wilhelm-Institut in Munich,[6] and compared with appropriate samples of Munich and rural Bavarian population.

The results of this investigation show that the net reproduction of schizophrenics and epileptics is distinctly less than that of the general

population in the same area and at the same time. This is due in part to high mortality after mental breakdown, but in still greater measure to the low marriage rates characteristic of the psychotic—both before and after the onset of mental disorders. The reduction of net reproduction rates due to these factors is negligible in the manic-depressive group, because of the late onset of manic-depressive disturbances.

Landis and Page, in their book, "Modern Society and Mental Disease," written in 1938, have carefully analyzed admission rates to mental hospitals and come to the conclusion that there is not any marked increase in mental disease either in the United States or in England, Belgium, Norway or France.

While natural processes thus appear to set limits to the reproduction of these defective stocks, the present number of the mentally sick is so great as to constitute the greatest single source of hospital expense and human suffering in this country today. But there is worse to come. Dr. Harold Dorn of the U. S. Public Health Service has recently shown that there will soon be a doubling of mental disease, assuming present rates for different ages, solely because of the increasing proportion of older people.

There is considerable evidence to indicate that hereditary factors affect susceptibility to many types of mental illness. Additional research is badly needed, but there are already strong grounds for discouraging the present practice of some psychiatrists of advising women patients that childbearing may improve their health. Such advice seems not only undesirable in the light of the genetic probabilities, but also because highly neurotic parents do not usually provide the optimum of home environment for the rearing of children. Here again, there is indicated an urgent need for research in medical genetics to determine more exactly the extent to which mental diseases may be related to hereditary factors, and to develop methods by which medicine can supplement the already favorable trends of natural selection toward the further reduction of this prevalent and expensive form of disease.

Changes in Age Composition

Present population trends make for rapid change in the proportion of persons in the different age groups. Estimates by Thompson and Whelpton indicate the following changes over a period of 100 years.

It is in the group of 65 years and over that the most striking change

TABLE

A CENTURY OF POPULATION TRENDS IN THE UNITED STATES, BY AGE GROUPS

Age	*1880*	*1930*	*1980**
Under 5	13.8	9.3	6.4
5-19	34.3	29.5	20.3
20-44	35.9	38.3	35.4
46-64	12.6	17.5	25.8
65 and over	3.4	5.4	12.1
Total	100.0	100.0	100.0

has been going on and will no doubt continue. While the proportion over 65 years of age may more than double in the next fifty years (5.4 per cent in 1930; 12.1 per cent in 1980), the change in absolute numbers is even more startling. These elders were over tenfold as numerous in the population of 1930 as in that of 1850, and may increase threefold over the present by 1980.[8]

In considerable part these changes in the proportion of persons at different ages result from the work of the medical profession; for it is not only the decline in births but also the conquest of infectious diseases which is piling up the number of those in the older groups. Thus, the solution of some of the most vital medical problems of infancy and youth has intensified a new set of problems, those connected with old age. Here new methods of attack are required. In the diseases of old age, changes in the patient's way of life may be necessary over long periods; the physician's care must be more continuous and personal, requiring more knowledge of traits of personality and family background. Hope for a rapid cure gives place to the desire to alleviate suffering and to extend the serviceable years of a mechanism beginning to wear out. In some ways these factors may seem to indicate an increasing need for the family physician rather than the specialist. On the other hand, early diagnosis is at a premium, together with a new emphasis on constitutional and genetic relationships, and here the advice of specialists would be important. Again, there is indicated the need for research in human genetics.

DIFFERENTIAL FERTILITY

To those engaged in the study of population, today's trends in births present a vivid picture of birth differentials. Persons living on the farm

* Estimated by Thompson and Whelpton.[7]

are, on the average, producing 50 per cent more children than the number needed for their replacement in the next generation; those in the great cities are 25 per cent short of enough births for replacement. The isolated and impoverished rural sections reproduce at an even higher rate—over large areas at 200 per cent of the rate required for replacement—while the more educated persons in the cities, say, at the upper high school level, are having only half of their replacement quota. For broad occupational groups the differences, while less extreme, are still striking, as shown by the following data from the U. S. Registration Area in 1928,[4] the replacement figure being taken at 1.00:

Professional	.76
Business and Clerical	.85
Skilled labor	1.06
Unskilled	1.17
Agricultural labor	1.32

Throughout the entire United States, with few exceptions, reproduction is highest among those most isolated, most limited in economic opportunities, most lacking in educational facilities.

Apparently differentials between occupational groups have been increasing since the middle of the 19th century, chiefly because of voluntary control of births, but also because medicine and sanitation have reduced differential death rates which formerly offset in part the reproductive effect of differential birth rates. In England and Wales, Notestein[9] finds that just prior to 1860 upper- and middle-class rates of reproduction were about 10 per cent below the rates for the country as a whole, and agricultural workers, who then—as now—headed the list, were less than 10 per cent above the nationwide average in reproduction, whereas, by the end of the century agricultural workers were almost 30 per cent above the average and the upper middle-class group almost 30 per cent below the average. Recently, there has been some evidence that these differentials have reached their furthest spread and are beginning to come together again. In the top income groups with the greatest economic security, there is a tendency to have somewhat larger families than those found among the next lower income ranks. In many European cities, the usual class differentials have been to some extent reversed in recent years. Those persons at the very bottom of the scale still have the most children, but from skilled workers up there is a slight increase as one goes to business executives, and the professional classes. But

this reversal has been brought about not by any increase in births at the upper levels, but by a decline in births in families at the lower occupational levels, so that reproduction as a whole is at a very low level. In Stockholm, for instance, the women of childbearing age are having only one-third of the number of children necessary for replacement. In this country the low record seems to be held by Portland, Oregon, with a rate of 50 per cent of replacement.

It seems likely that the trend in this country will be towards gradually smaller differentials between occupational groups. Such a trend is highly desirable for many reasons. At present a major part of the country's children are being born and reared in those American homes least able to provide adequate nutrition, adequate physical care or a stimulating educational environment. Thus in a real sense the work of public health and educational agencies has to be done all over again in every generation. Such a situation must go far to offset the great efforts now being made to raise the general level of public health and education. Those who are interested in improving the conditions of human life will want to hasten the natural trend towards a greater equalization of births.

The most obvious means of bringing about an equalization of births is to increase the availability of birth control and extend its use to all couples desiring to limit the size of their families, regardless of their economic situation or isolation. Quite apart from its other aspects, more effective use of contraceptives is probably the only practical alternative to abortion among many persons desiring to limit the size of their families. The medical profession can hardly escape its responsibility for directing the proper use of new methods of control over conception. Undoubtedly birth control will continue to be extended to persons to whom it is not now available, and as this process continues, there will be a further decline in the general level of births.

Under present conditions of American life, birth control alone would effect an equalization of births at a level of reproduction probably about half that needed for replacement. Such a low rate would be a denial of the nation's future. A permanent redistribution of births must be based not on birth control alone, but on birth control in combination with agencies which will increase births among competent parents who are able to give their children a decent physical, moral and mental environment, whatever social or occupational class they may belong to. Such an increase in size of family among competent people is essential not only to

offset the decline in births due to the increased use of contraception, but also to make the force of good home environments effective among a large proportion of the country's children. And there are a priori grounds for believing that an increase in size of family among competent people in all ranks of society is also essential for maintaining the genetic level of American stocks.

Forces Affecting Size of Family Among Competent People

Measures designed to increase births among competent people will be necessary to offset the further decline due to the extension of birth control. Such measures will undoubtedly include economic changes which will reduce the cost of having and rearing children. More free prenatal care, reduced maternity costs, and free health services for young children, seem almost certain items in the Nation's budget in the near future. But these and other measures for reducing the cost of children will not themselves lead people to have larger families. They are a preliminary to those changes in attitudes towards family life and children which can only be brought about by new types of impacts in the social and emotional environment. It will be no easy task to increase the desire for children among thoughtful people in our urbanized mechanical civilization. Every type of social agency will have to take part in such an effort. The greatest changes will perhaps be required in educational institutions which, until now, have given little thought to the effect of education on the development of the emotional life of the individual. But the most direct influences will be those effected in personal contacts. It is difficult to imagine any effective change in people's attitude toward having children without including doctors in the list of those taking an intelligent part in attempting such a change.

It is to the doctor that a woman first confides her hope that she is to become a mother. Does the doctor report the results of his examination with a laconic statement that she is in trouble, or does he strengthen her with the realization that this is the normal fulfillment of her feminine role, to the probable improvement of her health, and to her future happiness? If she has already several children, is his attitude one of admiration or of commiseration? Shortly she must decide whether her confinement is to take place in a hospital or in her home, and again she turns to her doctor. Is the doctor's advice weighted by consideration of where she will have the greatest comfort and pleasure in her baby, so that she may

look back on the first few weeks after the baby's arrival as a period of infinite happiness and charm? Will the nursing care and the environment during convalescence provide a favorable atmosphere? Students of population increasingly suspect that the attitude of the father often determines ultimate size of family. Does the doctor have this in mind, and do everything possible to bring the father into an intimate relation with the thrilling and beautiful aspects of bringing a new life into the world? Or is the father excluded at the start, and thus brought to think of this only as a period of anxiety and painful separation?

In the first week or so of the baby's life, the mother must decide whether she will try to nurse it herself or have it fed on a bottle. In advising her what she should do, does the doctor take into account those subtle emotional needs to which modern psychologists give such weight? The need of the mother for the full development of that relationship with her child, which may be weakened at its inception if she does not hold it in her own arms and feed it from her own breast. The need on the part of the baby for that warmth of security, that fullness of satisfaction, for lack of which its own emotional life may be in some degree stunted.

After the baby is weaned, family contacts with the doctor still continue. His attitude, and even sometimes his direct advice to both parents, will inevitably influence their decisions as to whether they should have additional children. Will the doctor in every case study these conditions, over and beyond the state of the mother's health, which affect the social desirability of their having more children; the home environment in which they will be brought up, the probability of their having a sound heredity?

These may seem strange questions to put to the members of the medical profession, pressed as they are by their present duties. But they do not seem strange questions to the student of population. The sterility of those who are most affected by modern civilization in this country and abroad is not in the main a physiological sterility. It is an emotional sterility, of which birth control is only the tool. We have created an environment in which the bearing and rearing of children is economically difficult, and concurrently we have both lessened the force of those influences in the environment which make for normal emotional development, and enormously increased the influences which make for the development of attitudes and values incompatible with the desire for children. That is

the picture as it appears to students of population in this country in recent years.

The medical profession by sanitation and the control of infectious disease has brought about an extraordinary decline in deaths. This decline in deaths has been accompanied by an extraordinary but highly unequal decline in births. A favorable distribution of births at present levels of reproduction would help stabilize recent advances in civilization and strengthen all efforts at further improvement. The question whether a favorable distribution of births can be aimed at a level sufficient for replacement presents one of the major problems of our present form of society. A clear understanding of this problem by the medical profession may be one of the deciding influences in its solution.

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IRRADIATION IN THE LYMPHOMATOID DISEASES*

LLOYD F. CRAVER

THE TERM lymphomatoid diseases embraces an extremely complex collection of morbid and mostly lethal processes. It is outside of the scope of this paper to discuss the few facts and the many theories concerning their causes, or to portray the wide scope of the pathologic changes which they may produce. There is no part of the human body entirely exempt from the possibility of being affected directly or indirectly by these diseases, and there is no age entirely immune from them. They concern therefore, every practitioner of medicine.

Even within the scope of any one of the so-called entities, such as Hodgkin's disease, variations are so great that each case becomes an individual problem for treatment. Yet they do have one thing in common in connection with treatment, and that is that irradiation by Roentgen rays or radium continues to be the single most effective method.

These diseases were among the first to be treated by irradiation, and even with the earliest crude techniques showed some remarkable responses. Yet they are so variable and unpredictable that their treatment by irradiation has remained an art rather than a science, to a degree greater than is true for many of the malignant tumors. In the treatment of some types of cancer, radiation is becoming one of the tools of the surgeon, used much as he might apply the knife or cautery. In malignant tumors affecting restricted parts of the body, for example epitheliomas of the lip, tongue, hypopharynx, skin and cervix, the radiant energy of radium and x-rays may be applied in a highly accurate manner, with rigid specifications of portal shape and size, direction of beam, amount and frequency of dose. Thus, the new type of specialist, the surgeon-radiologist, can develop a fairly standard technique, often combining a surgical procedure with a routine of irradiation that for a given type of cancer may be allowed to remain fairly fixed for a time long enough to permit

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judgment of results.

In the group of lymphomatoid diseases on the other hand, because of their great variations, it is hardly possible to devise a general routine, except perhaps for some of the commoner forms of local lesions, such as tonsillar lymphosarcoma, or Hodgkin's disease restricted to one or two groups of nodes. Yet the problem of determining the optimum technique of irradiation for these local lymphomatoid lesions is difficult. The ease with which regressions are secured by small doses may lead to a false sense of accomplishment, where much larger doses would be needed to effect actual sterilization of the disease. On the other hand, with large doses one may use up the patient's tolerance of radiation in producing regression of one lesion, only to find that other foci soon appear, and then the patient is less well able to withstand further irradiation.

Since we cannot hope to discuss all the possible variations of these diseases and consequent modifications of treatment even solely from the aspect of irradiation, let us therefore take up one by one the commoner types and indicate certain general plans of treatment. We must in advance recognize that cases must be individualized and that a given case may not fit neatly into these plans. We must also recognize that techniques of different workers vary considerably; that in these diseases, which are usually rather radiosensitive, widely different techniques may seem to give about equally good results; and that judgment about the value of a given technique is most difficult in such variable disease processes.

What I shall do here is to outline roughly our current preferences in modes of irradiation, with no claim that these methods are the best. There is no time here to discuss differential diagnosis, so we must assume in general that the diagnosis has been established, by biopsy if possible, and this we are doing routinely.

At this point we may consider briefly the types of radiation suitable for the treatment of these diseases. Beginning with Roentgen rays we have:

1. Low voltage Roentgen rays generated at or about 100,000 volts, suitable only for superficial lesions. These may be used unfiltered for very superficial lesions, or up to 4 or 5 millimeters of aluminum filter may be employed in order to screen out the longer, less penetrating wave-lengths and thus give a type of radiation suitable for lesions of some thickness on, in, or close under the skin.

2. Intermediate voltage Roentgen rays, generated at 140,000 to 160,000 volts, filtered by 3 to 6 millimeters of aluminium. Some workers prefer this type of irradiation even for deep seated lesions—rather illogically, I think, because there is too much effect on the skin and overlying tissues in proportion to what reaches deep parts.

3. High voltage Roentgen rays, usually generated at about 200,000 volts and filtered by 0.5 millimeters of copper or its equivalent. This gives adequate penetration to reach deep parts, and by increasing the target skin distance up to 70 or 100 centimeters or more a quite satisfactory depth dose is obtained without undue effect on the skin.

4. Super-high voltage Roentgen rays generated at 700,000 to 1,000,000 volts or more are probably entirely superfluous in the treatment of the lymphomatous diseases.

When low voltage and high voltage Roentgen apparatus is available, I see no great necessity for radium in the treatment of these diseases, except that extremely rarely there may be an indication for interstitial implantation of radon seeds or needles. Anything that can be done in this field by external application of the gamma rays of radium apparently may be done just as effectively and often more conveniently by Roentgen rays. We do at times use the 4 gram radium pack for external irradiation in place of the high voltage x-rays but not as a rule by preference.

Hodgkin's Disease

Given a case with an established diagnosis of Hodgkin's disease, two questions must be answered as well as possible before planning treatment. First, how extensive is the disease? Second, how acute a process does it seem to be? These questions can only be answered by a careful survey of the case, including history, physical examination, and roentgenographic studies. If, in a patient with very slight or no constitutional symptoms the disease seems to be limited to one group of nodes, as in the neck, one is probably justified in irradiating that area heavily in the hope of complete sterilization. At present we might give such a field 200 r daily or every other day to a total of 2000 r or more. Yet a word of caution at this point: experience in observing large numbers of cases of this disease suggests strongly that such a group of external nodes, apparently the only focus of the disease, is actually only an external sign of a process that gained entry to the body somewhere within the drain-

age territory of those nodes, and that therefore we must be on our guard against the possibility that the disease is already present elsewhere. Especially suspect are cases with a group of nodes at the base of the neck, in the axilla, or in the groin. Such cases call for careful examination of the chest and abdomen. When no internal focus can be found to account for the spread of disease to such an external group of nodes it may well be assumed nevertheless that the *noxa* of the disease, whatever its nature may be, has gained entry into the body at the appropriate internal site and has passed on, probably, however, leaving minimal undetectable traces internally. Therefore, in such situations the question always arises whether one should not give some treatment to the appropriate internal sites. For example, with a group of nodes situated at the base of the neck, in the position of the node of Virchow, even the absence of demonstrable disease in mediastinal or retroperitoneal territory would not exclude from our minds the advisability of giving some treatment to those regions. We do so in many cases but, because of the absence of demonstrable disease in those fields, we tend to give considerably smaller doses than we do to the known focus. We hope that the internal foci may actually be minimal and that smaller doses will serve at least to hold the process in check. We fear that larger doses might too greatly depress the patient's reserves and thus prevent us from giving full treatment if some other definite focus does appear.

To go back for a moment to the treatment of the mass of external nodes, I am by no means certain that the divided dose method of say 200 r every other day to a total of 2000 r is preferable. The dose of 200 r is about the upper limit of a single dose in the hands of most workers. However, some years ago we were giving such cases single doses of 400 to 600 r repeated at varying intervals for a few times. Some of the longest survivors we have had were treated by these fewer but larger doses, and therefore at the Fifth International Congress of Radiology in Chicago last year I ventured to raise the question whether such a method might not be preferable at least in some cases.

Many cases of Hodgkin's disease when first seen present more than one area requiring treatment, but are not yet in an advanced stage. In these cases each field is usually treated by 200 to 300 r every second or third day to a total of 1000 to 1200 r a field. Usually good regression will promptly follow such treatment.

Even cases that are far advanced may be greatly helped by judicious

irradiation. If severely anemic, such patients may be temporarily strengthened by transfusions so that they will better withstand treatment and obtain more good from it. When there are many areas of disease we usually do not try to treat all of them in one course, but select the larger and more important foci, giving them doses chosen empirically according to the bulk and depth of the lesions, and according to the condition of the patient. Some areas may receive 200 to 300 r two to five times at daily to weekly intervals, others about 400 r once. Then we may wait for three or four weeks, to give the patient a chance to get the benefit of this partial treatment. If we have been intelligent in our choice of areas and dosage, improvement may far exceed expectations, and then we have a patient better able to go on with further treatment. Literally, at times, patients with far advanced Hodgkin's disease seem to be pulled back from the brink of the grave by such measures, though at times our choice is not correct, or the disease is even worse than we thought, and we fail.

In some cases with widespread disease it may be well to include large fields such as the entire mediastinum, or the entire central abdomen or even greater sections of the trunk in single beams of radiation used at long target skin distances. Rather routine irradiation of large body fields is advocated particularly by Sluys of Belgium, Gilbert of Switzerland and Desjardins of the Mayo Clinic. I prefer to avoid routines and to choose areas according to the indications of the particular case.

Instead of irradiating the body in huge sections one may arrange the apparatus so that all or nearly all of the body may be irradiated at one time either in short individual sittings as is done in Europe and in a few centers in America, or at low intensity and continuously for days as we have done at Memorial Hospital in the unit named for Doctor Heublein, who suggested the latter method. In Hodgkin's disease irradiation of the entire body is used at Memorial Hospital only in small doses in selected cases and as a supplement to local irradiation. One cannot expect the body to tolerate enough exposure to radiation distributed simultaneously over its whole surface to produce satisfactory regression of bulky masses of granulomatous tissue. Yet, when the local masses and infiltrations have been treated we find in selected cases that by supplementing their treatment by small doses of general body irradiation, one gains frequently a tonic effect, with increase of weight and sense of well being, and freedom from recurrence of signs of disease activity for periods longer

than would otherwise be expected. We must freely admit that this statement is based on observation of numbers of cases, and that it is hardly possible to prove it by statistics. Even if some years from now unusually good survival figures appear among cases treated by general irradiation, one would have to take into consideration also the belief that the methods of local irradiation in the same cases had probably been more efficient. It has not seemed fair to restrict the treatment of any of these patients to general irradiation to see what it alone could do. Whether using general or local irradiation due regard must be had for the patient's tolerance, as judged both by his general state and by his blood count. If the white cell count becomes too low, say about 3000, it is usually best to suspend treatment for a time. However, it is important to point out that in some cases, in which no radiation has been used, a leukopenia will be found. As a rule one may proceed with irradiation in such cases, for it is probable that the low white cell count is caused by the disease, and that irradiation may actually be followed by a rise of the count to normal.

Hilar Tuberculosis and Hodgkin's Disease

In recent years several cases have presented themselves in which it has been very difficult to make a differential diagnosis between hilar tuberculosis and Hodgkin's disease or possibly lymphosarcoma. These are cases in which the Roentgen film shows distinct enlargement of hilar and tracheobronchial nodes of a pattern like that seen in the childhood type of tuberculosis, and in which no enlarged external nodes are available for biopsy. In such cases a negative tuberculin test is regarded as strongly suggestive that the process may be Hodgkin's disease, and accordingly that it may be safe to proceed with irradiation of the mediastinum and hilar nodes. It seems best to begin treatment cautiously, however, in order to test the response.

If, after a month or two a slight regression can be found, and if there has been no unfavorable reaction, it is considered safe to proceed with intensive irradiation, as for Hodgkin's disease.

As for results, we find 17 per cent of patients with histologically verified Hodgkin's disease surviving for five years or longer after treatment was begun. Certain workers report considerably higher five year survival figures than these. I feel that in such series there must have been a selection of cases accepted for treatment. Our figures apply to all cases coming to us in which the diagnosis was proved microscopically.

We reject only moribund patients and those who are under treatment elsewhere and come without permission of the physicians who are treating them. At one time recently we counted twenty-two patients living over five years, and we have now one patient who has survived over seventeen years. She was seemingly free of disease for about fifteen years but developed a mediastinal recurrence a few months ago. This was treated with fairly good response and she is still in good condition.

The most important factor of all in the treatment of Hodgkin's disease, or any of the lymphomatous diseases, is close vigilance for earliest signs of new foci or recurrences. Increased attention to the possibility of lesions of the lungs, bones, deep lymph node areas, nerve roots, spinal canal, and other tissues, leads to earlier detection, or to justified assumption of need for treatment of these parts, and thus to improved palliative results. Increased attention to such supportive measures as transfusions, iron, vitamins, and a general regime as for tuberculosis rewards us with better responses to irradiation and prolonged, more comfortable survival of our patients.

Lymphosarcoma

If in a case of lymphosarcoma the disease is apparently localized in one field, aggressive irradiation is justified in an attempt to cure. Usually such attempts fail, but there is a fair percentage of salvage among such cases, for long periods, if not actual cures. Yet here again we are dealing with variable, unpredictable processes and cases that seem bad may do well, while those that delight us by early complete regression may soon dismay us by the rapidity with which their disease returns and spreads.

In younger individuals, cases beginning as lymphosarcoma, sometimes apparently atypical and seemingly hardly more than an inflammatory process, regressing remarkably well under irradiation, may then rapidly develop a full blown picture of acute leukemia.

In cases of localized lymphosarcoma in which there appears to be a chance to secure complete sterilization, I feel that it may be a mistake to limit the size of the port to an area just large enough to include the palpable tumor, and to protract the treatment by giving small fractional doses daily. In this very cellular disease, tending to infiltrate widely, I believe it preferable to use ample ports and to give larger doses at a time. This is in contrast to the generally used procedure of small doses of low intensity repeated twice a day, daily or every other day to the same

port until a large total dose is attained – sometimes an epidermicidal dose. Some advocate large ports, others would treat lymphosarcoma as they do epidermoid carcinoma by ports kept as small as possible so as to include only the demonstrable part of disease. This is following the principle of treating cancer only where you find it, a principle which needs modification when we deal with lymphosarcoma. Yet we are finding that reticulum cell lymphosarcoma is not always nearly as radiosensitive as was once believed. When we find a case of localized lymphosarcoma that is relatively radioresistant it is probably better to use the protracted divided dose method, as in carcinoma, so that a much larger total dose can be given. In such a case I feel it would be advisable to restrict ports as much as possible for two purposes, first, to spare the patient the effects of as much irradiation of extraneous tissue as possible, and, second, to permit an increase of the dose to the tumor.

When a patient with lymphosarcoma has several widely scattered areas of the disease, obviously one must plan for the best palliation, rather than an attempt to cure. It then becomes a matter of proper choice of areas to be treated first, of individual and total dosage and the intervals between doses. In cases with widespread lymphosarcoma the use of the larger individual doses permits a more rapid coverage of most of the disease, while the protracted small dose method would necessitate a hopelessly long program. Just in this type of case in which the advocates of rigid adherence to that rule of treating cancer where you find it, using small ports and protracted dose methods, would tend to give up and say that such a case is better not treated at all, may be found some of the most worth while results of irradiation in palliation.

Results in Lymphosarcoma

Of 132 patients treated, 1918 to 1933, inclusive, in whom results can be determined, there were twenty-one or 15.9 per cent, who survived five years or longer. Five of these died after five years, while two are living over five years with evidence of disease, so that there are fourteen, or 10.6 per cent who survived five years or longer and who had been free of evidence of disease for six months, and in many cases much longer, ever since the regression that followed the first course of treatment.

Mycosis Fungoides

The superficial tumors and plaques of infiltration of the skin in this

disease are usually very radiosensitive in the beginning, and may yield readily to relatively small doses of low voltage x-rays. However, in many cases there is such widespread involvement of the skin that adequate treatment of all the disease would require more radiation than the patient could tolerate, so that each course of treatment must be restricted to the lesions that are most troublesome or threatening at the time. In later stages the recurrences that may appear in previously irradiated fields may be rather resistant, and lesions may appear in lymph nodes, bones, lungs and other viscera, requiring palliative treatment as for like lesions of advanced Hodgkin's disease or lymphosarcoma.

The Leukemias

In the treatment of leukemia by irradiation it is quite important to gauge the degree of acuteness or chronicity of the process clinically as well as hematologically. No sharp line of demarcation exists between acute and chronic forms but the more acute cases must be irradiated, if at all, with great caution. Even the more chronic cases may be greatly harmed by overenthusiastic treatment. Undoubtedly some leukemics have been killed by radiation effects. Yet judiciously applied radiation can be of benefit even in some cases apparently very acutely ill, and seemingly almost moribund.

It is especially in chronic myelocytic and chronic lymphocytic leukemia that irradiation plays a great part in bringing about restoration of the patient, for periods of varying length, to comparative or apparently complete health and economic usefulness. While statistics seem to show not more than a few months, possibly, of prolongation of life on the average, as compared with untreated cases, yet it seems evident that in some cases the inevitably fatal termination is considerably postponed by irradiation.

Chronic Lymphocytic Leukemia

The typical case of chronic lymphocytic leukemia presents a symmetrical general enlargement of external lymph nodes, commonly with some enlargement of liver and spleen and often with obvious enlargement of retroperitoneal nodes. The blood count may be typically leukemic, subleukemic or aleukemic.

In the typical case our preference is to irradiate first the external node masses, that is, each side of the neck, each axilla, and each groin. Each

such mass is given 100 to 300 r high voltage x-rays once, one area being treated at a time, and the patient being treated at intervals of one to three days depending on his condition. We then wait a few weeks, as a rule, to observe the effect on these external readily palpable masses, and the effect on the blood. Such a test cycle of treatment may be followed by considerable regression of the enlarged nodes and usually by a marked favorable change in the blood count. Anemia may disappear, the white cell count, if high, may fall to nearly normal, while the differential count may show a reversal of the polynuclear: lymphocyte ratio to nearly normal.

Further treatment then depends on the condition of the patient. If his blood count is nearly normal and if he has no marked internal masses of nodes or marked enlargement of spleen or liver it may seem best to withhold treatment until such time as the blood count or signs of leukemic infiltration in some area reveal the need for more treatment.

Unless some special feature appears, ordinarily the next course of irradiation is given to the mediastinal and retroperitoneal nodes. By taking a zone about 10 centimeters wide extending along the midline axis of the trunk, anteriorly and posteriorly, and dividing it into an upper, middle and lower third, one can irradiate the main bulk of these deep nodes. To each of these six portals (three anterior and three posterior) is given 100 to 300 r of high voltage x-rays. The individual doses and the intervals between them are chosen according to the condition of the patient.

Subsequent courses of treatment may consist of repetitions of these cycles to external or internal nodes, or both; or particular fields such as liver or spleen or deep inguinal and iliac nodes may demand special attention. The aleukemic forms are treated in the same way. In these cases, of course, the blood count is of less value, and one must depend largely on the responses of the known foci of disease. It would be quite misleading to gain an impression from this description of technique that a rigid routine is followed. Each case must be individualized and by no means all cases are treated in this way. For example, in the so-called splenic type of lymphocytic leukemia in which there is a large spleen with but little or no enlargement of lymph nodes, the treatment should begin by irradiation of the spleen.

Irradiation of the entire body has seemed to work very well in chronic lymphocytic leukemia and in some cases we choose to begin

the treatment by this method, and to rely mainly on it, using local irradiation rather as a supplement to care for especially prominent masses or infiltrations.

In the rare cases of lymphocytic leukemia in which no enlargement of liver, spleen, or lymph nodes can be found, one would naturally think of general irradiation as a logical procedure.

The emphasis, then, in the treatment of chronic lymphocytic leukemia is first on irradiation of lymph node areas, and second on irradiation of other foci of lymphocytic infiltration, wherever found. About 9 per cent will show a survival of five years or longer after treatment is begun as against the average survival of about two years, and some patients will live ten to twelve years or longer.

Chronic Myelocytic Leukemia

The typical case of this disease presents an enlarged spleen, sometimes of huge dimensions, frequently some enlargement of the liver, and as a rule practically a total absence of signs of enlargement of lymph nodes. The general run of experience indicates that best results, at least in the beginning, are obtained by irradiation of the spleen. This may be done by various methods. At Memorial Hospital we commonly use high voltage x-rays to large ports anteriorly and posteriorly over the spleen, giving 25 to 100 r at a sitting and treating daily or every other day to a total of about 300 r over each of the two ports. In some cases the radium pack is used, giving 2000 milligram hours or less at a sitting, at a radium skin distance of 10 centimeters, to a total of 6000 milligram hours anteriorly and posteriorly.

Such a course of irradiation may be followed by a transient increase in the leukocytosis, but in general, in about a month, a striking improvement will be found in the patient. He may gain weight, lose symptoms, present a marked shrinkage of the spleen, so that in some cases it may no longer be palpable, and his blood count may be restored so nearly to normal that it would be difficult to make a diagnosis of leukemia. In 3 weeks there may be an increase of a million red cells in the count.

Danger lies in overdosage of the more acutely ill patients. When external lymph nodes are enlarged, they may portend a more acute course. Signs of hemorrhagic tendency are danger signals, and indicate caution. Yet this bleeding tendency may disappear after irradiation.

Most of the writers state that it is advisable to be content to reduce

the white cell count to 20,000 or 30,000. If, however, our first cycle of treatment can succeed in bringing the count down to a normal level, I believe the patient as a rule will have a more nearly complete restoration to health for the time being and a longer interval before another course of treatment becomes necessary.

The blood count ordinarily gives the first sign that the disease is becoming active again and should be taken at intervals of seldom more than three weeks, at least at first. Further treatment is very much a matter of individualization. Some cases may carry on for years in response to repeated courses of irradiation given only to the spleen when it re-enlarges. In other cases special features arise, demanding special treatment. In some cases the blood count deteriorates again to a degree demanding more treatment at a stage when liver and spleen remain reduced to nearly normal size. At such times we consider either irradiation of the bones, especially spine, sternum, and proximal ends of long bones, or irradiation of the entire body in small dosage. We are especially likely to think of irradiation of the bones in cases in which pains are felt about the bones and joints.

In some cases the spleen fails to shrink satisfactorily after a few cycles of treatment have been given to the spleen; and even after further irradiation it remains large and firm. Some authors report shrinkage of these refractory spleens after irradiation of the entire body. We have not confirmed these observations, but see no reason to doubt that such an effect may be possible. Adjuvant methods of treatment such as administration of arsenic, heliotherapy and transfusions are regarded as outside the scope of this paper.

Results. Sooner or later every case becomes refractory to treatment. On the average these patients die in about two or three years after treatment is begun. Some survive exceptionally long periods, even up to fifteen or twenty-five years, but in these cases one feels that there is some exceptional factor promoting longevity and that the treatment may have had relatively little to do with the long survival. Only a small percentage (about 6 per cent) of the patients with myelocytic leukemia survive over five years after beginning treatment. The chief value of irradiation in this disease lies in the fact that it can bring about remissions repeatedly, to an extent which would not ordinarily occur, so that the patient, during his remaining span of life, short though it may be, enjoys periods of comparative health which otherwise he could not have.

Polycythemia Vera

Polycythemia vera or erythremia may be regarded as an analogue of myelocytic leukemia, that is, as a disease in which the red cell series rather than the granulocytic series is stimulated to increased activity. It has been advocated that in erythremia the enlarged spleen should be regarded as serving a protective function and that therefore it should not be irradiated; that, on the contrary, all the treatment should be directed to the bone marrow, which is the primary seat of the disease. The same argument might seem to apply to myelocytic leukemia, yet general experience has shown that in that disease irradiation of the spleen as a rule gives results superior to those obtained by treatment of the bones. However, in treating erythremia by local irradiation we do now as a rule, direct our radiation to the bones (spine, sternum and ends of long bones). Sgalitzer and others claim excellent results in erythremia by systematic total body irradiation. Sgalitzer reported good results in forty-two of forty-four cases, stating that in the recurrences one and one-half to five and one-half years later he obtained just as good response as in the first cycle of total irradiation, and that these recurrences took place much later than after the expensive, time-consuming cycles of local irradiation of multiple fields.

However, in this field there are certain cases termed erythroleukemia in which usually the dominating features at first are those of erythremia, but in which the spleen may be unusually large, the white cell count unusually high and the percentage of myelocytes in the blood count unusually great. In such cases the red cell count may fall after some months, so that instead of polycythemia the patient develops an anemia and then the features of myelocytic leukemia may begin to predominate. In such cases we find that treatment of the spleen may be more efficacious than treatment of bones in relieving symptoms.

Summary

In summary, the problems of treatment of the lymphomatoid diseases are many and complex, by reason of the great diversity of lesions in this group of maladies. Here are presented the main principles which currently seem to me best to follow in caring for the more typical forms by means of irradiation.

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BIOLOGICAL OXIDATION AND VITAMINS

Harvey Lecture, May 18, 1939

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As you know, the ultimate source of all energy, sustaining life, is the radiant energy of the sun. The energy of the sun's rays is captured by the green dyestuff of plants, the chlorophyl. This radiating energy cannot, as such, support life, for if it were essential, life would fail at night. Thus the energy is used to build up carbohydrate molecules from carbon dioxide and water, the excess of O being sent back into the atmosphere as O_2. In essence these carbohydrate molecules represent small parcels of energy, which can be stored and released by the cell according to needs. The "unpacking" of these parcels is the reverse reaction, in which the carbohydrate molecule is united again with oxygen to form carbon dioxide and water. This process we call oxidation or combustion. This oxidation is thus the ultimate source of all our energy. Since all cellular functions consume energy, oxidation is intimately connected with all activities of the cell and stands, so to speak, at the center of life.

During the last decades our conceptions regarding biological oxidation have been revolutionized and today oxidation represents one of the widest and most fruitful fields of biological research.

When speaking of oxidation we must always bear in mind one thing, i.e. that its purpose is to liberate energy and to liberate it in a form which can be used to maintain cellular functions.

Misled by the analogy of the steam engine, it was thought a few decades ago that in this process the molecule of foodstuff was simply attacked by oxygen, with the liberation of its energy in the form of heat. But there is this fundamental difference between the steam engine and our body: the latter is unable to use heat as a source of energy. Moreover, at the relatively low temperature of our body, oxygen does not attack the foodstuff molecule. It is evident that the process has to be activated in some way to take place at 37°C. It is natural that investigators looked first for an activation of oxygen, several active forms of oxygen being known to the chemist.

O. Warburg proved first that the oxygen is "activated" in cells. He studied the effects of cyanide, a poison which stops biological oxidation even at minimal concentrations. This substance has one peculiar property, and this is to form very easily coördination complexes with metal-atoms. Thus Warburg arrived at the conclusion that cyanide stops respiration by inactivating certain metal-atoms responsible for the activation of oxygen. These metal-atoms are linked to protein and these metal-proteids have the properties of an enzyme, the metal acting as the active prosthetic group. Warburg called this metal-proteid the "respiratory enzyme."

Somewhat later, H. Wieland, studying hydrogenation processes, arrived at another theory of respiration. It is known that organic molecules, having a double bond, can be made to take up hydrogen if treated with hydrogen in the presence of a catalyst, such as colloidal palladium. The metal combines with hydrogen and "activates" it. Wieland found that this process is reversible and H can also be detached from organic molecules in the presence of a suitable catalyst, if, instead of adding H_2 to the system we add a substance that is capable of binding H, i.e. an "H acceptor." Detaching H from an organic molecule is an oxidation. Wieland arrived at the conclusion that biological oxidations proceed in a similar way in oxidizing the organic foodstuffs, their H's being "activated" and detached, provided there is a suitable "H acceptor" present. Molecular oxygen, in Wieland's conception, is such an "H acceptor," while the foodstuff molecule itself acts as an "H donator." The activating enzyme we call "dehydrogenase" according to Thunberg's nomenclature. The place of the lost H's in the foodstuff molecule is taken by H-OH, water. In this way the molecule, by repeated dehydrogenation and hydration, becomes richer and richer in oxygen, until it is completely oxidized.

But how does all this work from the energy standpoint? We must remember that the aim of oxidation is in the first place the liberation of energy. The detaching of hydrogen from the organic molecule does not liberate energy. Neither does the introduction of water yield energy. The whole energy of oxidation is liberated in the oxidation of the hydrogen. It is well known that the oxidation of hydrogen is one of the greatest energy yielding reactions of chemistry.

These are quite simple statements but their consequences are rather far-reaching. They tell us that Nature knows, in essence, but one fuel and this is hydrogen. All our food is essentially but a fixed form of hydrogen and all the energy which supports life is derived from its oxidation,

with the formation of water.

We thus have the whole energy cycle: the plant cell, with its chlorophyl stores the energy of the sun, separating the elements of water, fixing the hydrogen to a solid carbon chain and sending the oxygen back to the atmosphere. All cells cover their energy need by reversing the process; taking the hydrogen from the organic molecule and uniting it again with the oxygen from the air.

It was thought at one time that the two theories, the theory of Wieland and the theory of Warburg, were contradictory. My first modest step in this domain was to show that there was no contradiction and that in the animal cell "activated oxygen oxidized activated hydrogen."

The next step of development is linked with the name of D. Keilin, who rediscovered certain hemin derivatives, found many years before by MacMunn. Keilin called these substances "cytochromes" and showed in classic experiments that they are substances involved in respiration. As Keilin taught us, there are three cytochromes, A, B and C. Cytochrome C has been isolated and shown to contain an iron atom. Probably the other two likewise contain iron. The metal atom is the active constituent of the molecule. In respiration this metal is alternately oxidized and reduced from its higher to its lower valency (ferric-ferrous). The three cytochromes are shunted in series: A is oxidized by Warburg's enzyme, A oxidizes C and C oxidizes B (Ball, Laki). Then cytochrome B oxidizes the hydrogen of the foodstuff, the "H donator." The H's of the foodstuff thus do not react immediately with the oxygen. Oxygen and hydrogen are separated by the series of cytochromes and Warburg's enzyme. The latter I will refer to as "cytochrome-oxidase," for its function is to oxidize cytochrome.

It is worthwhile to consider for a moment the implications of these findings. Of what does the oxidation and the reduction of a metal-atom consist? What is the difference, let us say, between ferrous and ferric iron? The difference is that the ferrous atom contains one more electron than ferric. When the hydrogen is oxidized by the Fe of cytochrome B it gives over its electron to the metal. The hydrogen itself acquires thereby a positive charge and becomes a hydrogen ion and unites with OH ions present in water. The electron added to Fe is then transferred from metal to metal, i.e. from cytochrome to cytochrome, then to the cytochrome-oxidase, to be transferred eventually to oxygen. The oxygen, after having taken up four electrons, can unite with four hydrogen

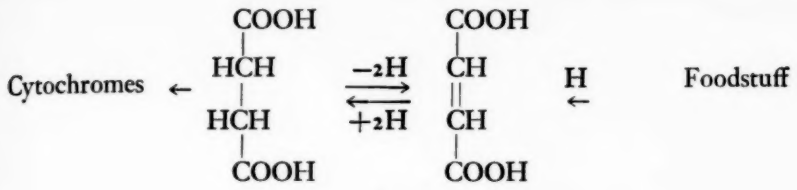


Fig. 1

ions of the water to become two molecules of water. There is thus in the cell a whole chain of electron transfers in which the hydrogen of the foodstuff serves as an "electron donator," the oxygen serves as an "electron acceptor," while the cytochromes with their oxidase serve as "electron transmitters." The role of oxygen in respiration is thus limited to accepting the electrons. At every step the electron itself liberates a certain quantity of its energy. On this series of electron transfers about two-thirds of the total energy of oxidation is liberated.

To sum up, the hydrogen of the foodstuff is activated by the specific enzymatic activators, the "dehydrogenases," yields its electron to cytochrome and is transferred through the series of metals to oxygen. From the investigations of Thunberg we know a number of such dehydrogenases, which could activate the hydrogen of different foodstuff molecules. But is it really the sole function of dehydrogenases to split off the hydrogen of the foodstuff molecule and make its electron available to cytochrome? This was the question I asked myself a number of years ago. Studying the enzymes of muscle I was struck by the fact that there was one among these dehydrogenases which had specific qualities. Its resistance and kinetics (O type) were extraordinary and its activity amazing. This dehydrogenase was the succinodehydrogenase, the dehydrogenase of succinic acid, discovered long ago by Thunberg. How were we to explain that Nature should produce such an extraordinary enzyme for succinate, when we had no reason to believe that succinic acid itself was one of the principal foodstuffs? Aided by my faithful collaborators, Banga, Gözsy, Huszak, Laki, Straub and others, I arrived at the conclusion that the function of this enzyme was not to split off H from a foodstuff but to transfer H from the foodstuff to cytochrome. Succinic acid is activated and dehydrated by this enzyme to fumaric acid, the two free valencies being joined in the form of a double bond (Figure 1). Fumaric acid is likewise activated by the same enzyme, the "succino-

dehydrogenase," so that it can bind by its double bond two new H atoms. The function of the acid and its enzyme would thus be to give off and take up H atoms alternately. The idea that dehydrogenases could also act as H transmitters was then somewhat revolutionary and needed support.

We have made a few observations which I think admit of no doubt, at least for muscle, of this function. First we looked for a substance that would inactivate the succinodehydrogenase in a selective way. If the succinodehydrogenase is a member of the chain of oxidation, as we supposed, the whole respiration would have to stop on its inactivation. J. H. Quastel's studies opened the way for the demonstration of such a specific inactivation. Quastel found that the succinodehydrogenase can be inactivated specifically by malonate. Malonic acid is the same substance as succinic acid, except it is one C atom shorter (Figure 2). It will thus take the place of succinate on the enzyme without being able to take on its function. By adding a small amount of malonate to respiring muscle we found that the whole oxygen uptake was stopped. We also found that, if the small normal store of succinate is washed out from the muscle, respiration stops and it starts again if the succinate is restored.

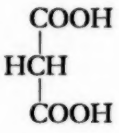
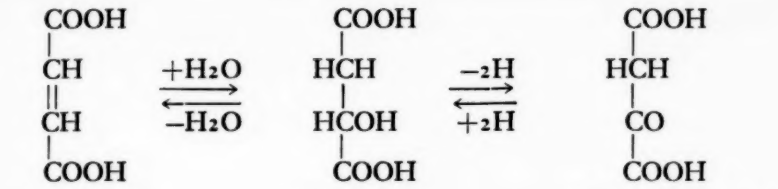


Fig. 2

The next step was to ascertain the position of the succinate in the mechanism of oxidation. We have found, and have been corroborated by D. E. Green, that succinate, activated by its dehydrogenase, could reduce cytochrome, but no other substance could do this. Other substances and dehydrogenases could reduce cytochrome only if succinate and succinodehydrogenase were present to transfer the hydrogen. Thus it became evident that the place of the succinate in the oxidation system was close to cytochrome, as shown in Figure 1.

But this was not all. H. Einbeck found more than twenty years ago that all animal tissues contained a very powerful enzyme which had the function of hydrating fumaric acid, that is to say, to add one molecule of water to its double bond and transform it into *l*-malic acid (Figure 3).



Fumaric acid Malic acid Oxaloacetic acid

Fig. 3

Not the whole fumarate is transformed in this way; the reaction stops when three-fourths of it is transformed. If we start out with *l*-malic acid, water is taken off until the same 1:3 equilibrium mixture is reached. Now what is the function of malic acid in the cell? There is a very powerful dehydrogenase present in muscle which will dehydrogenate malic acid, splitting off two hydrogen atoms, thus oxidizing malate into oxaloacetate. Oxaloacetate in turn will take up again any hydrogen coming from the foodstuffs. The series of events will thus be as follows: the foodstuff molecule is activated by dehydrogenase and passes over two of its H's to oxaloacetate, which is activated by the malicodehydrogenase. In this way the oxaloacetate becomes malate, which again passes on the H to fumarate. The fumarate then becomes succinate through the oxidation of the two newly acquired H atoms by the Fe of cytochrome. Then starts the chain of electron transport by the three cytochromes and their oxidase towards O_2. To sum this up we can say that the H mobilized goes through a series of reactions, is transferred from substance to substance, and yields energy at every step. Then, reaching cytochrome the H turns into an H-ion and its electron continues the journey. At the very end of the reaction we find both the respired O_2 and the H of the foodstuff in the form of water and it looks as if they had united directly. But this is, as we have seen, only an appearance. The H joined to the inspired O_2 is taken from water and so is the O which is eventually linked to the H derived from the foodstuff.

It is amazing to think that these simple four C atoms containing dicarboxylic acids should play such an important catalytic role in respiration. These substances seem to be one of the most important tools of living Nature. It was found recently by A. I. Virtanen that the same acids, in the form of oxaloacetate, play an important role also in N-fixation which

is one of the most fundamental chemical processes in Nature. As I will show you later, the same dicarboxylic acids probably also play a fundamental role in the respiration of plants.*

Further development in this field is linked with the discovery and analysis of the codehydrogenases. Some fifteen years ago I observed that certain dehydrogenases, as the dehydrogenase of lactic acid, acted only in the presence of a thermostable substance. This coenzyme was later purified in my laboratory and found to be a nucleotide. von Euler and Nilsson showed that Euler's "cozymase," likewise a nucleotide, was capable of acting as codehydrogenase. But real progress was made when Warburg discovered that this codehydrogenase contained a pyridine derivative, nicotinic acid amide. This pyridine acted as an H acceptor, one of its double bonds being hydrogenated. Apart from the succinodehydrogenase, all dehydrogenases acting in the main respiration cycle seem to need codehydrogenase.

These findings not only lengthen the known chain of oxidations but also throw a new light on the nature of dehydrogenases. We must now look upon a dehydrogenase, like the malic-, lactic- or triose-phosphoric-dehydrogenase, as upon a specific protein which is capable of adsorbing and activating simultaneously two substances, and of causing two H atoms to pass from one to the other. If we take the oxidation of triose-phosphate, the first thing that happens is that this sugar is adsorbed and activated by a specific protein, the dehydrogenase. At the same time the coenzyme is also adsorbed and activated, two H's pass from the sugar to the coenzyme and we obtain oxidized sugar and dihydro-coenzyme. Now the dihydro-coenzyme is adsorbed by the malicodehydrogenase together with oxaloacetate and the two H's pass from the dihydro-coenzyme on to the oxaloacetate and we obtain coenzyme and dihydro-oxaloacetate, i.e. malate. Now malate again gives its two H's to the coenzyme, and the coenzyme transmits them to fumarate.

At this point we get into difficulty, for the dehydrogenase that activates fumarate (the succinodehydrogenase) does not activate coenzyme.

* Lately the role of H transporters of the C_4 dicarboxylic acids has been denied by H. A. Krebs who believes that these acids act only as members in a more complicated cycle of carbohydrate breakdown. Krebs is of the opinion that oxaloacetate combines in muscle with an oxide of triose to citric acid, and the citric acid oxidizes to succinate. The succinate is oxidized to oxaloacetate, and the cycle begins again. I am unable to accept Krebs' generalization. Even if this cycle exists, it represents, as shown by Thomas, only an additional function of the C_4 dicarboxylic acids.

As I pointed out two years ago a member of the chain was missing at this point which had to transmit H from the dihydro-coenzyme on to fumarate. I suggested that this "something" might be a "yellow enzyme." These "yellow enzymes" are specific proteins which hold adsorbed a yellow alloxasine dye, which was observed first in my laboratory. Later it was shown by Warburg that these dyes acted in conjunction with specific proteins. Recently F. B. Straub, working in Keilin's laboratory, has isolated such an alloxasine protein which seems to answer all the requirements. Its exact place in the oxidation chain is not yet ascertained, but probably it is identical with the alloxasine protein, tentatively postulated two years ago between malate, the dihydro-coenzyme and fumarate, respectively. Straub's substance is also identical with the substance described by von Euler and Adler as "Diaphorase" and by Green and Dewan as "coenzyme factor." Unfortunately, time is too short to enter into detailed discussion of these catalysts, but I hope that this incomplete description brings out the point that the mechanism of biological oxidation represents a very complicated chemical apparatus of high complexity, specificity and precision. This mechanism liberates the energy of the H piecemeal, shifting the H atoms of the foodstuff molecule from substance to substance, then detaches the electron of H, and sends it through a series of metals to oxygen, liberating in this way the energy of the electron in appropriate small quantities fit to be used by the cell for its different functions.

I am hoping that you will forgive me if I do not present on this occasion an impartial review of the problems of oxidation, but instead present the development of the field from the narrow angle of my personal experience, giving undue prominence to my own work. To take this wholly personal outlook I must confess that in starting in this field some fifteen years ago my primary interest was not oxidation at all. What I really wanted to know was the function of the adrenal cortex. At that time we knew next to nothing about it. We only knew that man could not live without adrenals and turned brown before dying. You all know that one of the typical symptoms of adrenal cortical deficiency, or Addison's disease, is the brown pigmentation of the skin and mucous membranes. Now about half of the plants, including potatoes, apples, pears and bananas, do the same thing: they turn brown when dying. I have always been convinced of the fundamental chemical unity of living Nature and I thought that the brown pigmentation in dying plants and

in patients with Addison's disease might have a common chemical foundation. In regard to the pigmentation of plants we knew from Palladin's work that it is connected with the disturbance of biological oxidation systems. Consequently, I decided to take up the study of oxidation, hoping that if I understood oxidation better I also would understand the adrenal gland.

It was known that the brown pigmentation of dying plants was connected with the activity of a specific enzyme, a polyphenoloxidase which oxidized polyphenols, mostly catechol derivatives. Different theories were presented concerning the mechanism of this action. I was able to show that the enzyme simply oxidized the polyphenol into the corresponding diquinon, taking off its two H's (Figure 4). The diquinon, if not reduced with sufficient rapidity, combines with proteins or amino acids to form highly colored melanoid substances.

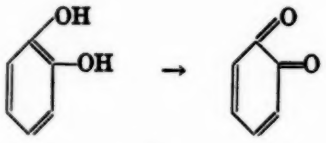


Fig. 4

The enzyme itself, the polyphenol, was lately isolated by Kubowitz in Warburg's laboratory and shortly afterwards by Keilin and was found to be a metal-proteid of copper.

This system, however, did not explain to me the function of the adrenal gland. So I turned the question around and did not ask why patients with Addison's disease turned brown, but why it was that we, who had normal adrenals, remained unpigmented. This could not be learned from the polyphenoloxidase plants, so I started to analyze the respiration of other plants which failed to turn brown when dying. About half of the plants, such as lemons and cabbages, do not turn brown when dying.

I soon found that the juice of these plants not only failed to turn brown itself but also prevented the juice of the polyphenoloxidase plants from turning brown, when the two juices were mixed. The inhibition was not complete, lasting only a few seconds, but was distinct. The analysis showed that this inhibition was due to the presence of a substance with peculiar properties which greatly fascinated me. The most striking

feature of this substance was its strong reducing power. It contained two very labile H atoms which explained the inhibition of pigment formation. By means of its two H's the substance reduced the quinols to phenol again, reversing the reaction shown in Figure 4.

The substance was crystallized and analyzed to a certain extent. I will not dwell upon details of its history for you all know it today as ascorbic acid, and you also know that it is identical with vitamin C. One of the most exciting phases of that research was the discovery of a rich source of ascorbic acid in Hungarian red pepper, the discovery of which made the preparation of several pounds of the pure vitamin possible. This substance was distributed to all workers desirous of investigating it, and their collaboration led in a short time to the complete analysis and synthesis of the vitamin. That highly spirited international collaboration of those days is still one of my pleasantest scientific memories.

Along with ascorbic acid I found in some plants an enzyme which could oxidize the acid in a reversible way and seemed to be involved, together with ascorbic acid, in respiration. The existence of this enzyme is denied in some quarters but I find it difficult to accept this conclusion.

This ascorbic acid oxidase has not yet been isolated. It is probably a Cu protein, as is the polyphenoloxidase.

To reduce O_2 to water we need four electrons and four H ions. Thus to reduce oxygen to water the enzyme would have to hold the O_2 molecule till it took up four electrons. Cu is unable to do this and will release the O_2 after it has taken up two electrons and two H ions, and is thus reduced to H—O—O—H, hydrogen peroxide. Whenever the oxidation of a substance like a polyphenol or ascorbic acid is catalyzed by copper or a copper-proteid there is a formation of peroxide. Accordingly, in the presence of ascorbic acid oxidase and polyphenoloxidase we find a second enzyme, a peroxidase, which will react with the peroxide and utilize this peroxide for the oxidation of a second molecule of catechol or ascorbic acid. To sum up: catechol-oxidase will oxidize two atoms of H from a molecule of catechol in the presence of O_2. The catechol is oxidized to quinon (Figure 4), while the O_2 is reduced to peroxide. $O_2 + C_6H_4(OH)_2 = H_2O_2 + C_6H_4O_2$. The H_2O_2 thus formed will react with peroxidase and oxidizes a second molecule of catechol: $H_2O_2 + C_6H_4(OH)_2 = 2H_2O + C_4H_4O_2$. The reaction in the case of ascorbic acid oxidase is analogous, except that the peroxide with the peroxidase will oxidize a phenol and the oxidized phenol in turn will oxidize a second molecule of

ascorbic acid. These phenols are specific, are members of the group of the yellow benzopyrane dyes studied by Kostanecky and Perkins, and are called, according to their structure, flavones, flavanoles or flavanones.

I have talked at such length about these reactions because we found that these dyes acting together with ascorbic acid also had a therapeutic potency which had certain characteristics of a vitamin action. We tentatively called these substances vitamin P. However, we were unable to demonstrate the vitamin nature conclusively in the animal experiments. Our own observations on guinea pigs were not corroborated. Beyond doubt the therapeutic action of these substances, which is capable of restoring the normal resistance of damaged capillaries, makes them available for the treatment of disease (vascular type of hemorrhagic purpura) for which medicine hitherto has had no remedy.

But to come back to oxidation, there was something disquieting in these results. In all systems hitherto discussed the action of O_2 was catalyzed by a metal or series of metals. The metal then oxidized reversibly two H atoms of an organic substance. In the muscle this substance was succinic acid. In certain plants it was catechol, in others ascorbic acid. It would be difficult to find three more heterogeneous substances and we were unable to give any reason why Nature selected these particular compounds for this end. Moreover, a greater uniformity was to be expected in such a fundamental process as oxidation. Another very disquieting matter was that in spite of all this work we did not know how plants really respired. I do not want to lose myself in details and will limit myself to telling you that there were serious reasons for believing that neither the polyphenoloxidase, nor the ascorbic acid oxidase were really involved in respiration and so we had no idea how plants respired, what the enzyme was which interacted in plants with O_2 and what the substance was on which this enzyme acted.

It became evident that something of basic importance was still to be learned. To find out what this was, my faithful collaborators and I set out to study the catalytic action of metals which catalyze the dehydrogenating oxidation of organic molecules. Such oxidations are catalyzed by metals outside the cells, and when the cell used metals to catalyze oxidation it did not invent a new principle; it merely applied an age-old reaction, but applied it in a very clever way: linking the metal to a specific protein in the cell and thus giving it a chance to act at its best.

There are two current theories to explain this catalytic activity of

metals. The one is the very complicated radical theory of Haber. The other theory is the simpler one. According to the latter the metal simply oxidizes the H of the organic molecule, taking over its electron. The metal thus reduced gives this electron in a second reaction to oxygen. To use different and simpler words, the function of the metal is to be alternately oxidized by the O_2 and reduced by the H. We found that none of these theories explained the changes and what really happened was that the metal combined, by its coördinate valencies, with the anion of the organic substance to be oxidized. By this combination both substances, the metal and the organic molecule, forming now a single molecule, are "activated." We obtain thus a complicated coördinative molecule in which the metal acts as a central atom. Now the valencies of this metal combine with a molecule of O_2. Both the O_2 and the organic molecule to be oxidized are built thus by the metal into a single molecule. Electrons are then transferred within this molecule via the metallic central atom from the organic molecule to the O_2. I will not go into the details of these reactions. The important matter is that the organic molecule, which is to be oxidized, has to answer very strict specifications. It must contain two OH groups at a certain distance, with a double bond between the C atoms holding these OH groups. The most suitable formation is the dienol grouping:

$$\begin{array}{l} -C-OH \\ \quad \| \\ -C-OH \end{array}$$

This formation is very unstable and thus very rare, and is found only in a very limited number of natural substances. One substance in which it is found is catechol, where it is stabilized by the aromatic cycle. Thus we are able to give an adequate reason why Nature applied catechol in this oxidation mechanism. Another substance, containing a dienol group, is ascorbic acid, in which the dienol is stabilized by the acid-lactone ring. Thus we can give the reason why Nature also applies this substance. At the same time the apparent heterogeneity of catechol and ascorbic acid disappears; in essence both are dienols.

There is a third relatively common substance containing the dienol group, dioxymaleinic acid, in which the dienol formation is stabilized by the two neighboring COOH groups (Figure 5). If all our ideas were correct we would have to expect that this substance is also employed by Nature in oxidation mechanisms. I shall now describe the last phases

of my most recent research. Experiments of Banga, Philippot and myself show that of the twenty-five plants examined all contain an oxidase for dioxymaleinic acid. In some plants the enzyme has a very striking activity. It is the most active oxidase known. There is reason to believe that in this enzyme we have found the way in which oxygen enters into vegetable respiration. Furthermore, we hope that this enzyme will shortly give us the explanation why Nature in animal cells utilizes succinic acid. If you compare the formulae of succinic acid (Figure 1) and dioxymaleinic acid you will observe that the two substances are closely related, dioxymaleinic acid being simply an oxide of succinic acid.

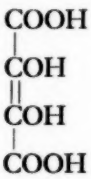


Fig. 5

I cannot cover my subject completely, nevertheless, I hope that I have made clear the great changes that have taken place during the last decades in our conceptions regarding biological oxidation. The field is hardly opened, but already it has given us a deeper insight into Nature's ways; it has yielded new substances, some of which are of vitamin nature and of great importance to health. I have discussed alloxasines, the dye component of yellow enzymes, substances connected with H transportation and dehydrogenation. The nicotinic acid amide of the codehydrogenases also acts as a member of the vitamin B group. Vitamin C was crystallized in the course of an analysis of vegetable respiration. The therapeutic action of Vitamin P was also discovered in the course of these experiments. I should also have mentioned Vitamin B_1, a substance which is closely connected with oxidative processes. Oxidation studies have thus not only helped us to reveal the existence of new active substances but have also given us information concerning their exact function and have taught us to regard vitamins no longer as mysterious bearers of life and health but as simple little wheels in this wonderful chemical mechanism, the perfect functioning of which we call simply life and health. These studies have also given us weapons for fighting disease and reducing human suffering, weapons not less sharp than the surgeon's knife.

THE DIAGNOSIS, TREATMENT, AND PREVENTION OF VITAMIN B_1 DEFICIENCY*

NORMAN JOLLIFFE

DIAGNOSIS

THE diagnosis of vitamin B_1 deficiency depends, at the present time, mainly upon a clinical evaluation of the history and the signs and symptoms presented by the patient. The clinical syndrome may be so typical that a positive diagnosis can be made; or so vague that it is difficult or even impossible to diagnose. It is hoped, however, that the clinician will soon have at his disposal a practical laboratory method to aid in the diagnosis.

The signs and symptoms attributed to vitamin B_1 deficiency are legion, the most definite being anorexia, fatigue, and a neurological and a circulatory syndrome. Anorexia and fatigue, are non-specific. In their presence the possibility of vitamin B_1 deficiency should be considered and confirmatory signs should be sought. When these symptoms occur without supporting objective signs, and do not definitely respond to thiamin therapy within seventy-two hours, they are probably not due to vitamin B_1 deficiency alone.

The neurological manifestations are those of bilateral and symmetrical polyneuritis involving first and predominantly the lower extremities. Peripheral neuritis that involves a single nerve, or that is not bilateral and symmetrical, or that does not involve first and predominantly the lower extremities is, in our experience, probably not due to vitamin B_1 deficiency alone. For such neuritides other etiologic agents should be sought.

For the purpose of clinical investigation we have classified the neurological manifestations according to severity into four groups: suggestive, mild, moderate, and severe. Heaviness of the lower extremities, and calf muscle cramps are usually the first symptoms.[1] These are followed by paresthesias in the toes and fingers, burning of the feet, and

* Read February 2, 1939 at The New York Academy of Medicine, in the Symposium on Vitamins with Special Reference to Therapy.
From the Department of Medicine, New York University College of Medicine, and the Medical Service of the Psychiatric Division, Bellevue Hospital, New York.

pain in the legs. It should be emphasized that pain, though nearly always present, can often be elicited only by a leading question. Calf muscle tenderness and plantar hyperesthesia are as a rule the earliest objective signs. The hyperesthesia may extend up the ankles and legs in a sock distribution. Vibratory sensation may be lost in the toes. These signs we classify as suggestive, and a positive diagnosis of polyneuritis is not made, as circulatory disturbances may cause these or very similar findings. When, however, in addition to these signs, the ankle jerks are absent, a diagnosis of mild polyneuritis can be made. As the deficiency continues, the sensory and motor changes advance, the knee jerks disappear, position sense in the toes becomes impaired, calf muscle atrophy develops, and foot drop follows. We classify this degree of involvement as moderate, provided the signs are confined to the lower extremities. When there is also involvement of the upper extremities, the spinal cord, or the cranial nerves; or when a "central neuritis" is present, we classify the polyneuritis as severe.

The circulatory manifestations of vitamin B_1 deficiency do not form a rigid clinical picture. They may occur in a person whose circulatory system is otherwise normal, or they may be superimposed on one previously damaged by degenerative, hypertensive, or inflammatory disease. These circulatory manifestations, as observed by Weiss and Wilkins,[2] Jones and Sure[3] and in our clinic,[4] may be classified as follows:

1. Edema and serous effusions occurring in the absence of congestive heart failure, enlarged heart, or recognized etiologic factors producing edema and serous effusions.

2. Edema and serous effusions occurring with supporting signs and symptoms of congestive heart failure, usually with definite roentgenographic evidence of cardiac enlargement.

3. Sudden circulatory collapse which may be the first manifestation of circulatory failure or may occur after other signs of circulatory failure are well advanced.

The circulatory manifestations of vitamin B_1 deficiency occur in about one-third of vitamin B_1 deficient subjects manifesting definite polyneuritis.[4] They are more likely to occur in subjects with suggestive or mild involvement than in those having advanced neuritis. This factor is related to the ability of subjects with mild neuritis to perform muscular exertion.

Some of the more characteristic diagnostic features of the circulatory

manifestations of vitamin B_1 deficiency are:

1. Mild nature of the polyneuritis.

2. Increased or normal velocity of the blood flow in the presence of congestive heart failure.

3. Rapid response to specific therapy with complete and permanent reversibility of the circulatory manifestations.

Vitamin B_1 deficiency should be suspected in the following groups of persons:

1. The indigent and low income groups. The average American diet affords a margin of safety in vitamin B_1 of 20 to 80 per cent.[5] This safety margin, though below the optimum, provides sufficient vitamin B_1 to protect against deficiency polyneuritis under ordinary physiologic conditions. As this diet is average, it follows that a considerable fraction of the American population must consume a superaverage and a considerable fraction a subaverage amount of vitamin B_1. That this is true is evident from calculations (Table I) made of the margin of safety of dietaries of families of wage earners and low salaried clerical workers living in industrial communities of the United States during 1934-36.[6] With the exception of one geographic group, families spending less than two dollars per week per capita for food are dangerously near or actually within borderline vitamin B_1/calory ratios. If this be true for wage earners, the indigent must consume even more of the cheap vitamin-free or vitamin-poor foods, such as sugar, white bread, rice, macaroni and other refined grain products.

2. Persons who have erroneous dietary habits and food idiosyncrasies. For example, the dietary history may reveal regular consumption of extradietary supplements of vitamin-free calories as obtained from sugar, corn syrup, alcohol, candy, pastries, or soft drinks, which may render a marginal diet inadequate. In evaluating the adequacy of a diet we must also scrutinize the dietary of any subject who remembers what he has eaten. The average person consuming a mixed dietary without food idiosyncrasies or restrictions rarely remembers this and is, therefore, probably consuming a varied diet. The more varied the diet, the less likely it is to be inadequate.

3. The alcohol addict. These subjects often consume amounts of vitamin-free alcohol sufficient to lower the vitamin B_1/calory ratio significantly, even if an otherwise adequate diet is maintained. A smaller consumption of biologically good calories, and impaired absorption or

TABLE I

MARGIN OF SAFETY IN VITAMIN B_1 OF DIETS OF WAGE EARNERS AND LOW SALARIED CLERICAL WORKERS IN RELATION TO WEEKLY EXPENDITURE ON FOOD AND GEOGRAPHICAL SECTION*

Region, number of families	*Weekly Exp. per food Const.*	VITAMIN/CALORY RATIOS *Thiamin* / *N.F.calory*	*Safety Margin* %	*Vitamin B_1* / *calory*	*Safety Margin* %
North Atlantic	1.33 – 1.99	0.308	+ 3	2.22	– 3
1394 white families	2.00 – 2.66	.329	+ 10	2.54	+11
	2.67 – 3.32	.370	+ 23	2.87	+25
	3.33 – 3.99	.320	+ 7	2.97	+29
	4.00 – 4.66	.404	+ 35	3.00	+31
Pacific	1.33 – 1.99	0.442	+ 47	2.85	+24
688 white families	2.00 – 2.65	.363	+ 21	2.67	+16
	2.67 – 3.32	.357	+ 19	2.95	+28
	3.33 – 3.99	.349	+ 16	2.69	+13
	4.00 – 4.66	.373	+ 24	2.84	+24
East South Central	0.67 – 1.32	0.256	– 15	2.30	– 0
426 white families	1.33 – 1.99	.327	+ 7	2.19	– 4
	2.00 – 2.66	.344	+ 15	2.37	+ 4
	2.67 – 3.32	.391	+ 30	2.57	+12
South	0.67 – 1.32	0.318	+ 6	2.00	–13
284 Negro families	1.33 – 1.99	.351	+ 17	2.31	+ 1
	2.00 – 2.66	.339	+ 13	2.40	+ 5
	2.67 – 3.32	.367	+ 22	2.69	+17
Sherman's Average American Diet		0.539	+ 80	2.74	+20
New York Budget Council	1.75	0.650	+113	3.08	+28

utilization of the vitamin, are additional factors leading to vitamin deficiency in these subjects.

4. Patients having diseases altering the vitamin B_1 requirement. The better known of these are listed in Table II. The primary factors that raise the vitamin B_1 requirement are increased total metabolism, reduced absorption of the vitamin from the gastrointestinal tract, and increased excretion of the vitamin following absorption.

* Reproduced through the courtesy of *New International Clinics.*[5]

TABLE II

FACTORS INCREASING THE VITAMIN B_1 REQUIREMENT*

I. Increase in Total Metabolism	*II. Faulty Assimilation*	*III. Increased Excretion*
A. Abnormal activity, as associated with	A. Diarrhea, especially of long duration, as in	A. Polyuria, as in
1. Prolonged strenuous activity	1. Ulcerative and mucous colitis	1. Uncontrolled diabetes mellitus
2. Delirium	2. Intestinal parasites	2. Diabetes insipidus
3. Manic depressive psychosis, manic type	3. Intestinal tuberculosis	3. Long continued excessive fluid intake, as in urinary tract infections.
	4. Sprue	
B. Fever, especially of long duration, as in	B. Gastrointestinal fistulae	B. Lactation
1. Tuberculosis	C. Diseases of liver or gall bladder	
2. Typhoid	D. Achlorhydria	
3. Malaria	E. Carcinoma of stomach	
C. Hyperthyroidism		
D. Pregnancy		
E. Rapid growth		

TREATMENT

The treatment of vitamin B_1 deficiency consists of rest, diet, vitamin B_1, and correction of the factors responsible for the deficiency.

Because of the danger of circulatory collapse on exertion, rest is essential for all subjects showing evidence of moderate or severe vitamin B_1 deficiency; complete rest if the patient has severe polyneuritis or shows circulatory manifestations. Before we realized the importance of absolute bed rest, we had a few unfortunate accidents, the sequel of which was sudden death. This danger apparently ceases after a short period of adequate treatment. We, therefore, confine these patients to bed the first few days. But after a few days of thiamin therapy the patient is made ambulatory as soon as possible, in order to prevent shortened muscles and to obviate much physiotherapy.*

During the last six years, working with Doctors Joffe, Colbert, Bowman, Goodhart, Rosenblum and Fein, we have attempted, among other things, to ascertain the most effective dose of vitamin B_1, the most effective route, and the various factors modifying the response to thiamin

* Reproduced through the courtesy of *New International Clinics.*[8]

chloride. For these studies we selected patients having a mild polyneuritis (the so-called "standard" subject), which, on the basis of history and of clinical characteristics, was thought to be due to vitamin B_1 deficiency.

We are aware of the hazards of drawing conclusions from therapeutic results. Improvement in these patients cannot as yet be gauged by a practical laboratory procedure. Furthermore, polyneuritis due to vitamin B_1 deficiency is a chronic disease, subject to wide variations in degree of involvement, occurring in subjects who frequently have a multiple rather than a single deficiency and in whom the pathologic changes, because of extent or duration, may be so far advanced as to be irreversible. For these reasons it was necessary to study a "standard" patient, whom we selected in accordance with the following criteria: there should be no clinical evidence of other deficiency disease; the signs of polyneuritis must be limited to the lower extremities, with the knee jerks preserved and with no obvious muscle atrophy or foot drop; the patient must show absent ankle jerks plus some demonstrable sensory changes, such as calf muscle tenderness, skin hyperesthesia in a peripheral nerve distribution, and impairment of vibratory or position sense. We judged the results of therapy on the basis of objective findings alone. To minimize interpretation, the tendon reflexes were recorded only as being present or absent, and sensory changes were recorded as to extent but not degree.

Since these studies have yielded useful hints concerning therapy, the results will be summarized:

1. Improvement in objective neurological signs of vitamin B_1 deficiency does not result when a patient is maintained with a diet consisting of a vitamin B_1/calory ratio of 1.7.[7]

2. When large amounts of vitamin B complex (vitamin B_1 free), nicotinic acid, or riboflavin are added to diets containing a vitamin B_1/calory ratio of 1.7 no improvement in objective neurological signs of vitamin B_1 deficiency occurs.[8]

3. With constant diets rich in the vitamin B complex, the rate and degree of improvement in the objective signs of polyneuritis vary directly with the vitamin B_1 intake.[7,9] This is illustrated in Table III.

4. Diets containing a constant amount of vitamin B_1, but rich in the entire vitamin B complex, apparently lead to a greater improvement in objective signs of polyneuritis than diets poor in vitamin B complex.[8]

5. The fraction of the vitamin B complex responsible for this enhanced action of thiamin is not known. We have evidence that it is not

TABLE III

THERAPEUTIC RESPONSE OF THE "STANDARD" PATIENT TO VARYING DOSES OF THIAMIN CHLORIDE

Vitamin B_1 as Thiamin Chloride	*No. of Days*	*Per cent Worse*	*Per cent Unchanged*	*Per cent Improved*	*Per cent Cured*
1 mg.	21	40	60	0	0
2 mg.	21	0	10	90	0
3 mg.	21	0	0	100	40
3 mg.	10	0	0	100	10
13 mg.	10	0	0	100	50

riboflavin or nicotinic acid, and that it is not present in the highly concentrated fractions of liver extract effective in pernicious anemia.[8]

6. Phosphorylated vitamin B_1 (or co-carboxylase) is apparently no more and no less effective than thiamin chloride.[8]

7. Administration of thiamin chloride by the intrathecal route possesses no advantage over the intramuscular or intravenous route.[8]

Using these facts gained from the study of our "standard" patients, and from the responses of our patients having moderate or severe manifestations of vitamin B_1 deficiency, we recommend the following dietary and specific treatment:

1. Insure that the diet is adequate in all respects. One of the best ways of doing this is to eliminate all vitamin-free or vitamin-poor foods such as white bread or crackers, pastries, alcohol, corn syrup, candy, corn starch, polished rice and soft drinks. Yet the diet must be one that the patient can eat, digest and assimilate. For patients who are extremely ill, the diet must be largely restricted to milk, cream, ground liver, pureéd legumes, thin whole grain cereals and fruit juices, administered if necessary through the nasal catheter in hourly feedings. Following improvement, or in less severely ill patients, whole wheat bread or crackers is added; the legumes need not be pureéd; other vegetables and raw and cooked fruit are added; and a wider variety of meats permitted provided that 250 grams of either liver or pork muscle are included in one of the meals daily.

2. Supplement the diet by vitamin preparations. These supplements should include daily 50,000 international units of vitamin A, 400 to 500 mg. of cevitamic acid, and a rich source of the entire vitamin B complex.

To insure the adequacy of the entire vitamin B complex, we routinely administer one of the following: 20 grams of vegex, 60 grams of brewers yeast, or 30 grams of aqueous liver extract. We would like to stress that vitamin concentrates, especially those in pill or capsule form, are possibly lacking either quantitatively or qualitatively in one or more of the fractions of the vitamin B complex.

3. Administer thiamin chloride in adequate amounts. The specific therapy should be administered parenterally, erring on the side of wasting the vitamin rather than giving a suboptimal amount. If the patient is in circulatory collapse or in severe congestive heart failure, large amounts of thiamin chloride should be given, up to 1000 mg. within the first twenty-four hours. The first dose may consist of 100 mg. intravenously and 300 mg. intramuscularly, with subsequent administration of 200 mg. intramuscularly every three to six hours. During the second twenty-four hours the dosage of thiamin chloride should be reduced to amounts recommended for the less severely ill patients. This latter group can be treated safely, depending upon severity, by administration of 50 to 200 mg. of thiamin chloride daily, preferably given in two doses, intramuscularly. After the patient is saturated with thiamin chloride, the amount of thiamin may be reduced to 10 mg. daily till convalescence is well established. Saturation may be recognized by the detection of a distinct odor resembling burnt rubber in the urine. Following convalescence, the balanced diet supplemented by rich sources of the vitamin B complex is sufficient unless a complication exists requiring an unusual amount of vitamin B_1, in which case thiamin chloride should be continued in amounts of 5 to 10 mg. daily.

The underlying cause primarily responsible for the deficiency must be found and if possible eradicated. It may be an inadequate diet, an underlying alcoholism, or some disease preventing the absorption or utilization of the vitamin.

Prevention

The prevention of vitamin B_1 deficiency consists of insuring an adequate intake of this vitamin. This problem may be met in at least three ways for the general population. The first and best solution would be the substitution of whole wheat bread and whole grain cereals for white bread and refined cereals, plus a reduction in our annual per capita consumption of vitamin-free sugar and vitamin-free alcohol.

A second possible solution would be the addition to vitamin B_1 deficient foods of enough thiamin chloride to bring the vitamin B_1/ calory ratio above borderline levels. Approximately 0.5 mg. of thiamin chloride for each 1000 calories would provide a sufficient margin of safety. The cost of this added thiamin to the manufacturers would probably not be in excess of one-quarter cent per 1000 calories. This method would not replace other nutritional factors removed in the milling and refining processes.

The third method would be for each individual consuming a suboptimal diet to take a daily supplement of either 2 mg. of thiamin chloride, or, preferably, a preparation of the entire vitamin B complex containing the same amount. The latter method would be impractical for a large portion of our population because of the expense of these preparations. The first two suggestions could be carried out with little added cost to the consumer.

The prevention of vitamin B_1 deficiency in persons in ill health consists of the recognition of the factors that alter the vitamin B_1 requirement, followed by the administration of prophylactic amounts of vitamin B_1. The administration of vitamin B_1 alone to those in ill health may not be sufficient, and we therefore recommend the use of the entire vitamin B complex plus 5 to 10 mg. of thiamin chloride daily, as well as other accessory elements of nutrition. In diseases interfering with absorption, the parenteral route should be utilized. A hitherto unrecognized danger exists of inducing vitamin B_1 deficiency in patients maintained with parenteral feedings of glucose, as in postoperative conditions. For such patients, this danger can be prevented by the routine administration of 5 to 10 mg. of thiamin chloride.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

FEBRUARY 2—*The New York Academy of Medicine.* Executive session—Reading of the minutes. ¶ Papers of the evening; Symposium on vitamins with special reference to therapy—a] Vitamin A, Arthur M. Yudkin, Clinical Professor of Ophthalmology, Yale University School of Medicine; b] Vitamin B, Norman Jolliffe, Assistant Professor of Clinical Medicine, New York University College of Medicine; c] Vitamin C, Gilbert Dalldorf, Director of Laboratories, Grasslands Hospital, Valhalla; Discussion by Arthur J. Patek, Jr., Soma Weiss, Boston, Philip Finkle. ¶ Report on election of members.

FEBRUARY 16—*The Harvey Society (in affiliation with The New York Academy of Medicine).* The Fifth Harvey Lecture, "The pathology of rickets with particular reference to the changes at the cartilage shaft junctions of the growing bones," Edwards A. Park, Professor of Pediatrics, The Johns Hopkins University School of Medicine.

MARCH 2—*The New York Academy of Medicine.* Executive session—Reading of the minutes. ¶ Papers of the evening—Symposium on arthritis—a] Gout, Philip S. Hench, Professor of Medicine, University of Minnesota (Mayo Foundation); b] The nature of hypertrophic arthritis (degenerative joint disease), Walter Bauer, Associate Professor of Medicine, Harvard University Medical School; c] Rheumatoid arthritis: The problem of diagnosis and treatment, Ralph H. Boots, Associate Attending Physician, Presbyterian Hospital; Discussion by Philip D. Wilson, Edward F. Hartung, Albert B. Ferguson. ¶ Report on election of members.

An exhibit was held in connection with the Stated Meeting. It was arranged by Dr. Albert B. Ferguson and consisted of various arthritides selected to compare and contrast the distinctive features of rheumatoid arthritis, osteoarthritis, gout, tuberculosis, suppurative arthritis and gonococcic arthritis in various states of these diseases and at various joints with particular reference to their differences

in type of destruction, decalcification, calcification and soft tissue reaction.

MARCH 16—*The Harvey Society (In affiliation with The New York Academy of Medicine).* The Sixth Harvey Lecture, Distribution of enzymes in tissue and cells, K. Linderstrom-Lang, Carlsberg Laboratory, Copenhagen.

APRIL 6—*The New York Academy of Medicine.* Executive session—a] Reading of the minutes; b] Election of Trustee. ¶ The fourteenth Hermann Michael Biggs memorial lecture was delivered by Mr. Frederick Osborn, Research Associate in Anthropology, American Museum of Natural History on "The significance to medicine of present population trends." ¶ Report on election of members and corresponding fellows.

APRIL 20—*The Harvey Society (in affiliation with The New York Academy of Medicine).* The Seventh Harvey Lecture "Genic and hormonal factors in some biological processes", C. H. Danforth, Professor of Anatomy, Stanford University.

MAY 4—*The New York Academy of Medicine.* Executive session—a] Reading of the minutes; b] Presentation of diplomas. ¶ Papers of the evening—Symposium on recent advances in the treatment of peripheral vascular disease—a] Clinical manifestations (25 min.), Irving S. Wright, Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; b] Medical treatment (25 min.), Edgar V. Allen, Assistant Professor of Medicine, University of Minnesota (Mayo Foundation); c] Surgical treatment (25 min.), Reginald H. Smithwick, Assistant in Surgery, Harvard Medical School; Discussion, Beverly Chew Smith (8 min.), James C. White, Boston (8 min.). ¶ Report on Election of Members.

MAY 18—*The Harvey Society (in affiliation with The New York Academy of Medicine).* The Eighth Harvey Lecture, "Biological oxidation and vitamins," Albert Szent-Györgyi, Professor of Medical Chemistry, University of Szeged, Hungary.

SECTION MEETINGS

FEBRUARY 3—*Surgery.* Papers of the evening—a] The Miller-Abbott tube as an adjunct to surgery of small intestinal obstruction, Octa Leigh and John A. Nelson (by invitation), Discussion by Henry Graham; b] The use of vitamin K and bile salts in the prevention and control of the bleeding tendency in obstructive jaundice, Kenneth B. Olson (by invitation), Discussion by Robert Moore; c] The treatment of staphylococcus septicemia with bacteriophage, Alfred Longacre and Helen Jern (by invitation), Discussion by Ward MacNeal; d] The study of wound healing of transverse and vertical incisions in 400 operations on the biliary tract, John Gius and Howard Barkley (by invitation), Discussion by Beverly Smith; e] Electro-Thermic coagulation of aortic aneurysm, Arthur H. Blakemore (by invitation), Discussion by Robert Levy.

FEBRUARY 7—*Dermatology and Syphilology.* Presentation of cases—a] Vanderbilt Clinic; b] Miscellaneous cases. ¶ General discussion. ¶ Executive session.

FEBRUARY 7—*Pediatrics.* Presentation of case—Adjustment problems in an adolescent boy, Norvelle C. LaMar (by invitation). ¶ Round table discussion—The problems of adolescence, Herbert B. Wilcox, *Chairman,* Beatrice M. Kesten, Norvelle C. LaMar (by invitation), Howard C. Taylor, Jr., and by invitation: Mr. Lawrence K. Frank, Vice-President, The Macy Foundation, Mrs. Millicent Carey McIntosh, Principal, The Brearley School, Mr. James I. Wendell, Headmaster, The Hill School.

FEBRUARY 14—*Neurology and Psychiatry.* Reading of the minutes. ¶ Papers of the evening—a] Further investigation on affect and skin temperature, Bela Mittelmann (by invitation), Harold G. Wolff, Discussion by Frank Fremont-Smith, Paul Schilder; b] Electroen-

cephalography and pneumencephalography—a comparative study, Leo M. Davidoff, Margaret Rheinberger (by invitation), Discussion by Cornelius G. Dyke, Kurt Goldstein (by invitation), Armando Ferraro, Foster Kennedy; c] A new approach to the treatment of epilepsy, Manfred Sakel (by invitation), Discussion by Foster Kennedy, Emanuel D. Friedman, Irving H. Pardee.

FEBRUARY 15—*Otolaryngology.* Reading of the minutes. ¶ Papers of the evening—Peroral endoscopy—a] Inception and development, M. C. Myerson; b] Anesthesia, R. L. Moorhead (by invitation); c] Bronchoscopic clinic, David Jones; d] Indications for 1. Laryngoscopy and bronchoscopy, Rudolph Kramer; 2. Esophagoscopy, gastroscopy and duodenoscopy, Charles J. Imperatori; e] Contraindications and accidents, John D. Kernan; f] Single and biplane fluoroscopy, F. M. Law; g] Pneumograms, technic and interpretation, George R. Brighton.

FEBRUARY 15 — *Genito-Urinary Surgery.* Reading of the minutes. ¶ Case reports—a] Ruptured aortic aneurysm, simulating renal tumor, Saul J. Pearlman (by invitation); b] Carcinoma of the adrenal cortex with adrenocortical syndrome, Report of two cases, Joseph Tenenbaum. ¶ Paper of the evening—Renal, perirenal and pararenal suppurations, John Duff, Discussion by Joseph A. Hyams, Howard S. Jeck, Paul Aschner, Gordon Oppenheimer, Isadore Rubin. ¶ General discussion.

FEBRUARY 17—*Orthopedic Surgery.* Reading of the minutes. ¶ Presentation of cases. ¶ Papers of the evening—a] Subdeltoid bursitis treated by aspiration and vascularization, Joseph E. Milgram, Discussion by Leo Mayer; b] Painful shoulders, Robert L. Patterson; c] Value of electrical treatment of subdeltoid bursitis, Norman E. Titus. ¶ General discussion. ¶ Executive session.

FEBRUARY 20—*Ophthalmology.* Examination of cases, 7:00 o'clock (bring instruments). ¶ Reading of the minutes, 8:15. ¶ Case reports—a] Contact glass correction of monocular aphakia with binocular single vision, A. E. Town (by invitation); b] Fuchs absorption stripes of the cornea, Joseph Laval; c] Subconjunctival injections of neo-prontosil in the treatment of eye infections, R. Townley Paton; d] Altitudinal hemianopsia associated with absence of radial pulse bilateral, H. W. Brown (by invitation); e] Relation of vascular disease to retinitis. A new clinico-pathological study (with slides), S. A. Agatston; f] Unilateral lachrymation associated with chewing, Philip Adalman (by invitation); Discussion by Morris Bender (by invitation); g] Herpes zoster ophthalmicus (left), Frances Richman (by invitation); h] Keratoconjunctivitis with pannus associated with acne rosacea, Conrad Berens, Paul McAlpine (by invitation); i] Fundus presentation with retinitis striata, Olga L. Sitchevska (by invitation); j] Bilateral cystoid detachment of the retina, A. L. Kornzweig (by invitation); k] Paralysis of the superior rectus in Graves' disease, Saul Miller (by invitation); l] Optic neuritis of rhinologic origin, Morris Jaffe; m] A cyst in the vitreous, Frank LaGattuta (by invitation).

FEBRUARY 21—*Medicine.* Reading of the minutes. ¶ Papers of the evening—a] Mechanism of nephritis induced by antikidney serum, Joseph E. Smadel, Rockefeller Hospital (by invitation), Discussion by Lee E. Farr, Rockefeller Hospital (by invitation); b] Acute nephritis in relation to hemolytic streptococcus infection, John D. Lyttle, Discussion by A. R. Dochez; c] The renal and vascular sequelae of glomerulonephritis, George Baehr, Discussion by Dana W. Atchley.

FEBRUARY 28—*Obstetrics and Gynecology.* Presentation of cases—a] Repair of prolapse in the senile without anesthesia (two cases), David N. Barrows. ¶ Papers of the evening—a] A modification of the Manchester operation (illustrated by motion pictures), Paul A. Younge, Boston (by invitation), Discussion by Robert T. Frank, Harvey B. Matthews;

b] Management of breech presentation, read by Christopher J. Duncan, Brookline (by invitation), Discussion by James A. Harrar (by invitation), William E. Studdiford. ¶ General discussion.

SURGERY. Instead of the regular meeting on March 3, the Section of Surgery held a combined meeting with the Section of Medicine on March 21,

MARCH 7—*Dermatology and Syphilology.* Presentation of Cases—a] Skin and Cancer Unit of Post-Graduate Medical School; b] Miscellaneous cases. ¶ General discussion. ¶ Executive session—Appointment of Nominating Committee.

MARCH 7—*Joint Meeting, Neurology and Psychiatry and the New York Neurological Society.* Papers of the evening—a] Colloid tumor of the third ventricle with a concomitant large sella turcica, with necropsy findings, M. Neustaedter, Theodore Meltzer (by invitation); Discussion by Joseph H. Globus; b] Observations on the position of the motor cortex in man, obtained through electrical stimulation, John E. Scarff; Discussion by Foster Kennedy; c] Frontal lobectomies in the treatment of tumors in the anterior cranial fossa, Byron Stookey; Discussion by M. H. Teitelbaum (by invitation), Richard Brickner, Ira Cohen. ¶ Executive session—Section of Neurology and Psychiatry, Appointment of Nominating Committee.

MARCH 8—*Historical and Cultural Medicine.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one Member of Advisory Committee. ¶ Papers of the evening—a] Medicine and Surgery—Its study and practice in the United States before 1860, William C. Clarke, Cornwall Bridge (by invitation); Discussion by Paul B. Sheldon, Hugh Auchincloss; b] Nathan Smith and cancer therapy, Ashley W. Oughterson, New Haven (by invitation); Discussion by Cornelius P. Rhoads. ¶ General Discussion.

MARCH 9—*Pediatrics.* Symposium on treatment of bone injuries in infancy and childhood presented by the staff of the fracture service of the Presbyterian Hospital. ¶ Reading of the minutes. ¶ Papers of the evening—a] Fractures of the clavicle, Harrison L. McLaughlin (by invitation); b] Supracondylar fractures, Frederick M. Smith (by invitation); c] Reliance on growth correction of deformities, Barbara B. Stimson; d] Epiphyseal injuries, Clay Ray Murray, e] First aid treatment, William Darrach. ¶ General discussion. ¶ Executive session—Appointment of Nominating Committee.

MARCH 15—*Genito-Urinary Surgery.* Reading of the minutes. ¶ Case reports—a] Chorioepithelioma of bladder, J. M. Szilagyi (by invitation); b] Solitary kidney with anuria (three cases), Leo Edelman, H. E. Leiter (by invitation); c] Diverticulum of female urethra, H. E. Leiter (by invitation); d] Uretero-vesical reimplantation of ureter, Abraham Hyman; e] Perirenal insufflation, William H. Mencher; f] X-ray control for operative treatment of renal calculi, G. Oppenheimer, g] A new medium for retrograde pyelography, M. Swick (by invitation). ¶ General discussion. ¶ Executive session—Appointment of Nominating Committee.

MARCH 15—*Otolaryngology.* Instead of the regular meeting of the Section of Otolaryngology on March 15, at the Academy, the members of the Section were invited to a joint meeting with the College of Physicians of Philadelphia. ¶ Papers of the evening—a] Speech hearing, Douglas MacFarlan; Discussion by Edmund P. Fowler; b] Sensitization reactions as observed microscopically in the living mammal, Elliot R. Clark, Eleanor Linton Clark, Richard G. Abell, Ph.D., Harry Schenck; Discussion by Marvin F. Jones.

MARCH 17—*Orthopedic Surgery.* Reading of the minutes. ¶ Presentation of case—Hemiphalangectomy in hallux valgus and hallux rigidus, Albert J. Schein; Discussion by Seth Selig, Robert Lippmann. ¶ Papers of the evening—a] Tubercu-

lous arthritis. Study of 100 operated cases, B. M. Bosworth; Discussion by Mather Cleveland; b] Slipped femoral epiphysis treated by ambulatory spica, Max S. Rabinowitz; Discussion by Samuel S. Kleinberg; c] Results of amputation for tuberculous knee foci, E. M. Winant; Discussion by Arthur Krida. General discussion. ¶ Executive session—Appointment of Nominating Committee.

MARCH 20 — *Ophthalmology.* Instructional Hour — After cataract, Webb Weeks. Slit Lamp Demonstration, Milton L. Berliner, Wendell L. Hughes, Girolamo Bonaccolto, Gordon M. Bruce. ¶ Reading of the minutes (8:30). ¶ Presentation of cases—a] Aspiration of the anterior chamber for glaucoma and other diseases of the eye, Conrad Berens; b] An unusual case of retained intraocular foreign body, Edgar P. Sherman (by invitation); c] Bilateral congenital ectopia lentis, Edgar P. Sherman (by invitation); d] Contralateral transillumination, Henry Minsky; e] Cysticercus cellulosis in the vitreous, Clyde E. McDannald. ¶ Paper of the evening—Further studies of the Canal of Schlemm and its anastamoses, Georgiana Dvorák-Theobald (by invitation). ¶ Executive session — Appointment of Nominating Committee.

MARCH 21—*Combined Meeting, Medicine and Surgery.* Papers of the evening—Medical and surgical aspects of the gastric ulcer problem—a] Natural history and diagnosis of gastric ulcer, T. Grier Miller, Philadelphia (by invitation); b] The indications for surgical therapy of gastric ulcer, Fordyce B. St. John; c] Discussion: (1) Pathology of gastric ulcer, Nathan C. Foot, (2) The x-ray in the control of treatment, R. E. Pound, (3) Medical management, Howard F. Shattuck, (4) Surgical procedures, Condict W. Cutler, Jr.; d] Open discussion. ¶ Executive session—Appointment of Nominating Committee.

MARCH 28—*Obstetrics and Gynecology.* Presentation of case—Unusually large tumor of the vulva, Joseph Q. Jonas (by invitation). ¶ Papers of the evening—a] Sulphanilamide treatment of gonorrhea in the female, Emily D. Barringer and Staff, Kingston Avenue Hospital; Discussion by E. A. Horowitz (by invitation), B. H. Schoolnik (by invitation); b] Intravenous basergin in the third stage of labor (Report of 1500 cases), Edward J. Davin (by invitation); Discussion by S. J. Scadron; c] Analysis of maternal deaths and hospital obstetrical statistics in New York County; Report of the Committee on Maternal Welfare, Max Schneider (by invitation); Discussion by George W. Kosmak, Charles A. Gordon (by invitation), John L. Rice, Alfred M. Hellman. ¶ Executive session—Appointment of Nominating Committee.

APRIL 4 — *Dermatology and Syphilology.* Presentation of cases—a] City Hospital; b] New York Polyclinic Hospital; c] New York Hospital & Cornell Medical College; d] Miscellaneous cases. ¶ General discussion. ¶ Executive session—Nominations of Section Officers and one member of the Advisory Committee.

APRIL 7 — *Surgery.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of the Advisory Committee. ¶ Presentation of papers—a] The appendix stump: its manner of healing both in the open and closed methods of treatment, Isidor Kross; Discussion by Percy Klingenstein; b] The importance of early diagnosis and treatment in acute appendicitis, Bronson S. Ray; Discussion by George J. Heuer; c] The severer forms of acute appendicitis with special reference to appendiceal abscess, Ernest E. Arnheim; Discussion by Eugene H. Pool; d] Methods of drainage in appendicitis, F. Stafford Wearn (by invitation); Discussion by Edward W. Peterson. ¶ General discussion.

APRIL 11—*Neurology and Psychiatry.* Papers of the evening—a] Vertebral fractures as a frequent complication in Metrazol therapy, Phillip Polatin (by invitation), Murray M. Friedman (by invitation),

Meyer M. Harris, William A. Horowitz (by invitation), Nolan D. C. Lewis (by invitation), Clay R. Murray; b] Psychological factors in migraine, Herman Selinsky; Discussion by Abraham Kardiner, Harold G. Wolff, Lewis Stevenson, Emanuel D. Friedman, George Hyslop, Bela Mittleman (by invitation); c] Case of cerebral "Pseudo Abscess" of otogenic origin, Emanuel D. Friedman; Discussion by E. Miles Atkinson (by invitation), Charles Davison, Richard M. Brickner; d] Sex taboos, sex offenders and the law, Joseph Wortis; Discussion by Donald Shaskan (by invitation), Ruth Benedict (by invitation), Adolf Meyer, Israel Strauss. ¶ Executive session—Nomination of Section Officers and one member of Advisory Committee.

April 13—*Pediatrics.* Reading of the minutes. ¶ Papers of the evening—a] Fatal lead poisoning in a nursing infant due to prolonged use of lead nipple shields, Murray H. Bass, Sidney Blumenthal (by invitation); Discussion by John Caffey, Benjamin Kramer, Charles Hendee Smith; b] The use of tetanus toxoid in private practice, Robert Page Rogers; Discussion by Edith M. Lincoln, Samuel Z. Levine, Abraham Tow; c] Puberty in the male; Physical development and endocrinopathies, William A. Schoenfeld (by invitation); Discussion by Robert T. Frank; d] Medical care of the non-hospital case of contagion, with special reference to the care of whooping cough, Harry O. Zamkin (by invitation); Discussion by Bela Schick. ¶ Executive session — Nomination of Section Officers and one member of the Advisory Committee.

April 17 — *Ophthalmology.* Instructional hour — Plastic surgery, Wendell L. Hughes. ¶ Slit lamp demonstration, Milton L. Berliner, Wendell L. Hughes, Girolamo Bonaccolto, Gordon M. Bruce. ¶ Executive session—a] Reading of the minutes (8:30); b] Nomination of Section Officers and one member of Advisory Committee. ¶ Presentations—a] A new implantation sphere made of vitallium, William Brown Doherty; b] Postoperative report on a case of meningioma producing unilateral exophthalmos, James W. Smith. ¶ Paper of the evening The role of states of anxiety in the pathogenesis of primary glaucoma, Mark J. Schoenberg; Discussion by Smith Ely Jelliffe, Joshua Rosett, F. Fremont-Smith.

April 18 — *Medicine.* Executive session — Nomination of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—a] Acute changes in the early lesions of pulmonary tuberculosis, Wm. H. Stearns, 7B Service of Bellevue Hospital (by invitation); Discussion by J. Burns Amberson; b] A practical method of visualizing the chambers of the heart and the thoracic blood vessels in man, George P. Robb, Department of Therapeutics, N. Y. U. College of Medicine (by invitation), Israel Steinberg, 3rd Medical Division, Bellevue Hospital (by invitation); Discussion by Arthur C. deGraff; c] Coarctation of the aorta with mycotic aneurysm in a child of ten years, Gertrude H. B. Nicolson (by invitation); Discussion by F. Elmer Johnson.

April 19—*Genito-Urinary Surgery.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Paper of the evening—The treatment of bladder pain—Moving picture demonstration, Carlisle F. Schroeder, Detroit, Michigan (by invitation); Discussion by John H. Morrissey, Fred McClellan (by invitation), Simon A. Beisler. ¶ General discussion.

April 19—*Otolaryngology.* Executive session —a] Reading of the minutes; b] Nominating of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—Acute contagious diseases —ear, nose and throat complications— a] Otitis, Alfred Schattner (by invitation); b] Upper respiratory, Arthur Wilson; c] Pneumothorax and emphysema—lantern slides, Morris E. Stern

(by invitation); d] Lower respiratory, Jesse Bullowa; e] Poliomyelitis, Philip Stimson; Discussion by Harry Neffson, Wallace Hamilton, Vera V. Dolgopol.

April 21—*Orthopedic Surgery.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Presentation of case—Cases illustrating first paper of the evening, E. Arnheim. ¶ Papers of the evening—a] A study of scoliosis following empyema, based on a study of all empyema cases admitted to the wards of the Mount Sinai Hospital from 1932 to 1936, inclusive, Seth Selig, E. Arnheim; Discussion by Harold Neuhof; b] Motion picture illustrating internal rotation brace treatment of early coxa anteverta, Henry Milch; c] (1) Motion picture illustrating results in the use of the angle plate, (2) Lantern slides of the Hawley table in the treatment of fractures of the lumbo-dorsal and cervical spine, George W. Hawley (by invitation), Ralph D. Padula (by invitation); d] Osteomyelitis—acute and chronic (comparison of the end results of cases treated postoperatively with Dakin's solution, Orr method or bacteriophage); Discussion by Robert L. Preston, Fred H. Albee, Mather Cleveland. General discussion.

April 25—*Obstetrics and Gynecology.* Executive session — Nomination of Section Officers and one member of Advisory Committee. ¶ Presentation of case—Congenital absence of vagina — operation, Milton Bodenheimer. ¶ Papers of the evening—a] Obstetrics in a general hospital (10,000 cases at the Bronx Hospital), J. I. Kushner (by invitation); Discussion by Hervey Williamson; b] Roentgenology: An aid in obstetric diagnosis and choice of treatment, Julius Jarcho; Discussion by Arthur S. Unger, William E. Caldwell, Alfred M. Hellman. ¶ General discussion.

April 28—*Special meeting of the section of Dermatology and Syphilology.* The second special meeting of a symposium on syphilis was held at the Academy. There was inspection of cases from 7:30 to 9:00 o'clock, after which, a discussion open to all practitioners followed. ¶ Cases of the following were presented: Cardiovascular syphilis, cerebrospinal syphilis, neurosyphilis, visceral syphilis, eye syphilis.

May 2—*Dermatology and Syphilology.* Executive session — Election of Section Officers and member of Advisory Committee: For Chairman, Elias W. Abramowitz, for Secretary, Lewis B. Robinson, for member of Advisory Committee, Leo Spiegel. ¶ Presentation of cases—a] Beth Israel Hospital; b] Sea View Hospital; c] Miscellaneous cases. ¶ General Discussion.

May 2—*Combined Meeting, Neurology and Psychiatry and the New York Neurological Society.* Papers of the evening—a] Treatment of a case of ulcerative colitis associated with hysterical depression, George E. Daniels (by invitation); Discussion by Clarence Oberndorf, C. V. Burt (by invitation); b] Developments in the psychoanalytic conception and treatment of the neuroses, Sandor Rado (by invitation); Discussion by George E. Daniels (by invitation), David M. Levy (by invitation), Smith E. Jelliffe; c] Psychiatric study of some miraculous cures at Lourdes, Smiley Blanton (by invitation); Discussion by Abraham A. Brill, Carl Binger (by invitation), Smith E. Jelliffe. ¶ Executive session. Election of Section Officers and member of Advisory Committee: For Chairman, Lewis D. Stevenson, for Secretary, Samuel Brock, for member of Advisory Committee, Morris Grossman.

May 3—*Otolaryngology.* ¶ Executive session. a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: For Chairman, Jacob L. Maybaum, for Secretary, Page Northington, for member of Advisory Committee, Francis W. White. ¶ Presentation of cases—a] Primary carcinoma of middle ear and mastoid; recovery after operation and radiation. Postoperative results of endaural modified radical mastoidectomy, Clarence H. Smith; b] Mastoiditis masked by the administra-

tion of sulfanilamide, Samuel Rosen; c] Otitic hydrocephalus, Harry Rosenwasser; d] Lateral sinus thrombosis—unusual course, Louis Hubert. ¶ Case Reports—a] Squamous cell carcinoma of the nasopharynx and the petrous pyramid, Joseph G. Druss; b] Needle in aorta (Lantern Slides), Bilateral empyema (Leptothrix), David H. Jones. ¶ Papers of the evening—a] Experimental evidence of gonadotropic hormone in nasal and sinus mucous membranes, A. A. Eggston; b] The nasogenital and auro-genital relationships, Hector Mortimer, Montreal (by invitation).

MAY 5—*Surgery.* Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: For Chairman, J. William Hinton, for Secretary, Grant P. Pennoyer, for member of Advisory Committee, Frank L. Meleney. ¶ Presentation of cases—a] 1. Lobectomy for multiple chronic lung abscesses. 2. Total chronic empyema; broncho-pleural fistulae; multiple stage Schede thoracoplasty, Alexander E. W. Ada; Discussion by John V. Bohrer; b] Two cases illustrating pneumonotomy for putrid abscess of the lung, Harold Neuhof; Discussion by Arthur S. W. Touroff. ¶ Papers of the evening—a] Surgical therapy in pulmonary tuberculosis, Louis R. Davidson; Discussion by Howard Lilienthal; b] Non-tuberculous pulmonary suppuration, Carl Eggers; Discussion by Girard Oberrender; c] Closure of the large empyema cavities, Frank B. Berry; Discussion by Richmond Moore (by invitation). ¶ General discussion.

MAY 10—*Historical and Cultural Medicine.* Executive session—a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: For Chairman, Louis Casamajor, for Secretary, Ramsay Spillman, for member of Advisory Committee, Howard Reid Craig. ¶ Papers of the evening—a] Medicine in Utopia, Herbert Silvette, University of Virginia (by invitation); Discussion by Ramsay Spillman; b] The curious career of Typhoid Mary, George Albert Soper (by invitation); Discussion by F. Warner Bishop. ¶ General discussion.

MAY 11—*Pediatrics.* Case demonstrations. Executive session—Election of Section Officers and member of Advisory Committee: For Chairman, Rustin McIntosh, for Secretary, Leslie O. Ashton, for member of Advisory Committee, Philip M. Stimson. ¶ Presentation of single case reports—a] Willard Parker Hospital; Pertussis and pyloric stenosis (unoperative), Frank S. Cross (by invitation); b] Babies Hospital; Progressive myositis ossificans, Donovan J. McCune (by invitation); c] St. Luke's Hospital; A case of influenza meningitis with recovery, Frederick H. Wilke; d] Lenox Hill Hospital; A case of precocious sexual development in a male child, aged three and a half years, Frederick Castrovinci (by invitation; e] New York Post-Graduate Hospital; Vaccinia with interesting features, Irving Posner (by invitation); f] Metropolitan Hospital; Pneumococcus meningitis treated with sulfapyridine, Irving Weinstock (by invitation); g] Roosevelt Hospital; Case of non-pneumococcal pneumonia simulating typhoid fever, John Landon; h] Polyclinic Hospital; Rupture of the stomach in the new born, Abraham Tow; i] The Mount Sinai Hospital; Addison's disease in a boy of twelve, George J. Ginandes (by invitation); j] New York Hospital; Purulent arthritis in an infant, John Washington (by invitation).

MAY 15—*Ophthalmology.* Instructional Hour—Allergic manifestations of the eye, W. C. Spain. ¶ Slit lamp demonstration—Milton L. Berliner, Wendell L. Hughes, Girolamo Bonaccolto, Gordon M. Bruce. ¶ Executive session—a] Reading of the minutes (8:30); b] Election of Section Officers and member of Advisory Committee: For Chairman, David H. Webster, for Secretary, Robert K.

Lambert, for member of Advisory Committee, James W. White; c] Reports of Committees. ¶ Presentations—a] Pseudoglioma due to hyperplasia of Bergmeister's papilla, Ralph I. Lloyd, Arnold deVeer (by invitation); b] Tangent curtain ruler, Loren Guy; c] Congenital anomaly of the optic nerve head, Sidney A. Fox (by invitation); d] Acute exudative chorioditis treated with vasodilator, Walter Duggan (by invitation); e] A case of foreign body (piece of of steel) in the optic nerve, Hugh S. McKeown, William P. McGuire (by invitation); f] Neurofibromatosis with pulsating exophthalmos (illustrated by colored movies), Wendell L. Hughes; g] Intraocular foreign bodies. Some comments based on 120 consecutive cases, Elbert S. Sherman; h] Angiomatosis retinae, Edward P. Ryan (by invitation).

MAY 16—*Medicine.* Executive session—Election of Section Officers and member of Advisory Committee: For Chairman, Samuel W. Lambert, Jr., for Secretary, Oswald R. Jones, for member of Advisory Committee, Thomas T. Mackie. ¶ Papers of the evening—a] Some comments upon the existence of arteriosclerosis in birds and the infra-human mammals, Herbert Fox, Philadelphia (by invitation); Discussion by Charles R. Schroeder, D.V.M. (by invitation); b] Cholesterol atherosclerosis, Kenneth B. Turner; c] Studies on the pathogenesis and the production of lesions of the arteries, Milton C. Winternitz, New Haven (by invitation); Discussion by Harrison S. Martland.

Genito-Urinary Surgery. The following were elected at the April meeting of the Section: Simon A. Beisler, Chairman, John H. Morrissey, Secretary, Fedor L. Senger, member of Advisory Committee. There was no meeting of the Section in May due to the meeting of the American Urological Association in White Sulphur Springs, West Virginia.

MAY 19—*Orthopedic Surgery.* Executive session—a]Reading of the minutes; b] Election of Section Officers and member of Advisory Committee: For Chairman, David M. Bosworth, for Secretary, Lewis Clark Wagner, for member of Advisory Committee, Joseph B. L'Episcopo. ¶ Papers of the evening—a] Compression of cancellous bone. Manifestations in the head and neck of the femur. Treatment by drill-channels—with lantern slides, Eugene J. Bozsan (by invitation); Discussion by Leo Mayer, Walter Galland; b] Pathology and operative correction of certain deformities of the fingers, Emanuel B. Kaplan (by invitation); Discussion by Leo Mayer; c] A method of reduction of fractured neck of femur by transtrochanteric skeletal traction, to be followed by axial fixation with threaded steel pins, David R. Telson (by invitation); Discussion by Nicholas Ransohoff. ¶ General discussion.

MAY 23—*Obstetrics and Gynecology.* Executive session—Election of Section Officers and member of Advisory Committee: For Chairman, Alfred M. Hellman, for Secretary, Frank Smith, for member of Advisory Committee, David N. Barrows. ¶ Papers of the evening—a] Laboratory findings and interpretation in eclampsia, Leon Chesley (by invitation); Discussion by R. G. Douglas (by invitation); b] Extraperitoneal cesarean section—Presentation of a new technique with motion picture demonstration, Edward G. Waters (by invitation); Discussion by Alfred C. Beck, Albert H. Aldridge. ¶ General discussion.

AFFILIATED SOCIETIES

New York Roentgen Society. There was no meeting held in February.

FEBRUARY 23—*New York Pathological Society.* Case reports a] Glomus tumor of the arm, Andrea Saccone, Joseph Mendeloff, Metropolitan Hospital (10 minutes); b] The effect of intravenous sucrose on the kidney, Paul Klemperer, Mount Sinai Hospital (10 minutes). ¶ Papers of the evening—a]Pathological findings following therapeutic hyper-

thermia, Louis Lichtenstein, Hospital for Joint Diseases (20 minutes); b] Hemostatic mechanisms as a cause of visceral lesions, Abraham Penner, Alice Bernheim, Mount Sinai Hospital (30 minutes). ¶ Executive session.

MARCH 20—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* Papers of the evening—a] The treatment of ovarian carcinoma, William Harris, Robert I. Walter (by invitation), Arnold L. Bachman (by invitation); b] Post-irradiation changes in the lung; a clinical, roentgenological and pathological study, with emphasis on the late and terminal stages, Jacob R. Freid, Henry Goldberg (by invitation). ¶ Discussion by Howard C. Taylor, Jr. (by invitation), Harriet C. McIntosh. ¶ Executive session.

MARCH 23—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* ¶ Case reports—a] Multiple plasmoma of the small and large intestine, Chester R. Brown (by invitation) and Amour F. Liber (by invitation), Lincoln Hospital; b] Post-traumatic (but not post-fractural) rarefaction of long bones, Henry L. Jaffe, Hospital for Joint Diseases. ¶ Papers of the evening—a] Spontaneous tumors of rabbits and their transplantation in the same and in alien species, Harry S. N. Greene (by invitation), Rockefeller Institute for Medical Research, Princeton, New Jersey; b] Sarcomas of the trachea, Tobias Weinberg, Mount Sinai Hospital. ¶ Executive session.

APRIL 17—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* Papers of the evening—a] The roentgen diagnosis of myocardial infarction; (1) The roentgenkymographic findings, Marcy L. Sussman; (2) Correlation of the clinical course and electrocardiographic findings with the roentgenkymographic findings, Simon Dack (by invitation); (3) The fluoroscopic diagnosis, Arthur M. Master (by invitation); Discussion opened by Bernard S. Oppenheimer (by invitation); b] X-ray visualization of soft structures of pregnancy, William Snow; Discussion opened by Ross Golden. ¶ Executive session.

APRIL 27—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* Program arranged by the New York Post-Graduate Hospital. Case reports—a] Xeroderma pigmentosum, D. S. D. Jessup; b] Acquired right-sided parasternal diaphragmatic hernia, R. A. Colmers (by invitation); c] Pulmonary atresia and "tetralogy of Fallot", L. H. Meeker. ¶ Papers of the evening—a] Prolonged hyperpyrexia with necropsy, W. J. MacNeal, H. H. Ritter (by invitation), S. M. Rabson; b] Experimental endocarditis due to infection with streptococcus viridans, M. Wasseen (by invitation), M. J. Spence (by invitation), W. J. MacNeal. ¶ Executive session.

MAY 15—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* Papers of the evening—a] Physical factors of low voltage short distance Roentgen ray therapy (contact therapy), Carl B. Braestrup (by invitation); Irving H. Blatz (by invitation); b] Recent experiences with low voltage short distance Roentgen therapy (contact therapy), William Harris. ¶ General discussion opened by: L. D. Marinelli (by invitation); George T. Pack. ¶ Executive session—a] Election of officers; b] General business.

MAY 25—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* Case reports—a] A case of true hermaphrodism, Milton Helpern, Medical Examiner's Office (10 min.); b] Rhabdomyoma of the uterus, N. C. Foot, New York Hospital (10 min.). ¶ Papers of the evening—a] Perineurial fibroblastoma, rather than Schwannoma. A histological study, I. M. Parlov, Jewish Hospital of Brooklyn (30 min.); b] Absorption and utilization of Vitamin K. Studies in experimental animals and in man, Robert A. Moore, William DeW. Andrus, Jere Lord, Isabel Bittinger, Cornell University Medical College (30 min.). ¶ Executive session.

DEATHS OF FELLOWS

ALOFSIN, LOUIS MARK: 448 West 34 Street, New York City; born in Russia, October 22, 1883; died in New York City, May 31, 1939; graduated in medicine from the Long Island College Hospital in 1907; elected a Fellow of the Academy November 6, 1930.

Dr. Alofsin was a Fellow of the American Medical Association, a member of the Alumni of the French Hospital and a member of the County and State Medical Societies.

FAULKNER, EBENEZER ROSS: 101 East 58 Street, New York City; born in Glenholme, Nova Scotia, January 28, 1876; died in New York City, May 25, 1939; received the degree of Bachelor of Arts from Dalhousie University, Halifax, Canada in 1897 and graduated in medicine from that University in 1901; elected a Fellow of the Academy, November 3, 1910.

Dr. Faulkner had been surgical director of the Manhattan Eye, Ear and Throat Hospital and consultant to the French Hospital, Yonkers General Hospital, and St. Joseph's Hospital of Far Rockaway. For several years he was professor of laryngology and rhinology at the Polyclinic Hospital.

Dr. Faulkner was a Fellow of the Royal College of Surgeons of England, a Fellow of the American Medical Association, a diplomate of the American Board of Otolaryngology and a member of the American Academy of Ophthalmology and Otolaryngology, the New York Otolaryngological Society, the American Laryngological Association, the American Laryngological, Rhinological and Otological Association, and the County and State Medical Societies.

LAMBERT, ALEXANDER: 43 East 72 Street, New York City; born in New York City, December 15, 1861; died in New York City, May 9, 1939; received the degrees of A.B. in 1884 and Ph.B. in 1885 from Yale University; graduated in medicine from the College of Physicians and Surgeons, New York, in 1888; elected a Fellow of the Academy May 2, 1893.

Dr. Lambert was professor of clinical medicine at Cornell University Medical College, 1898-1931; attending physician to Bellevue Hospital, 1894-1933; and assistant bacteriologist to New York City Department of Health, 1894-1901. It was largely on Dr. Lambert's initiative that the Doctors Hospital was founded and he was president of the medical board of that institution at the time of his death.

Dr. Lambert was a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association and its president in 1919, a member of the Association of American Physicians, and a member and former president of the State Medical Society.

Dr. Lambert was a Colonel in the Medical Auxiliary Corps of the U. S. Army, having served in France from 1917 until the end of the War. While in France he headed the Medical Division of the American Red Cross.

In the biography of General Gorgas by Marie D. Gorgas and Burton J. Hendrick, Dr. Lambert is credited with saving the official head of Dr. William C. Gorgas as director of the sanitary work during the building of the Panama Canal.

STUBENBORD, WILLIAM: born in Germershein, Bavaria, Germany, September 29, 1851; died in New York City, May 23, 1939; graduated in medicine from New York University Medical College in 1879; elected a Fellow of the Academy March 3, 1887. Dr. Stubenbord was a member of the County and State Medical Societies.

WARD, GEORGE HAROLD: 240 Engle Street, Englewood, New Jersey; born in Napanee, Canada, August 16, 1879; died in Blairstown, New Jersey, May 30, 1939; graduated in medicine from Queen's University, Kingston, Ontario, Canada in 1903; elected a Fellow of the Academy November 3, 1910.

Dr. Ward was chief of the eye, ear, nose and throat division of the Englewood, Holy Name and Teaneck Hospitals and consultant to the Nyack and Rockland County Hospitals. He was a member of the State and County Medical Societies.

ANNOUNCEMENT

THE ROBERT LIVINGSTON SEAMAN FUND

The New York Academy of Medicine announces the establishment of "The Robert Livingston Seaman Fund for the furtherance of research in bacteriology and sanitary science," with six hundred dollars available for assignment in 1939. This fund has been made possible by the terms of the will of the late Dr. Robert Livingston Seaman and will be administered by a committee of the Academy of Medicine under the following conditions and regulations:

1. The committee will receive applications from either institutions or individuals during the summer and up to September 15, 1939. Communications should be addressed to Dr. Wilson G. Smillie, Chairman, 2 East 103 Street, New York City.

2. The fund will be expended only in grants in aid for investigation or scholarships for research in bacteriology or sanitary science. The expenditures may be made for:

   A. Securing of technical help.

   B. Aid in publishing original work.

   C. The purchase of necessary books or apparatus.